A randomized control trial comparing the efficacy oforal Clonidine as premedication versus Dexmedetomidine infusion in the peri-operative period, on anaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion.

This dissertation is in partial fulfillment of the requirement for the M.D. Degree (branch X) Anaesthesiology examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in April 2013.

CERTIFICATE

This is to certify that this dissertation **"A randomized control trial to comparing the efficacy of oral clonidine premedication with Dexmedetomidine infusion in the perioperative period, onanaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinalfusion."** is an original research work done by Dr. Hari Narayana Prabhu A towards partial fulfilment of the requirements for the award of MD Anaesthesiology degree.

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INTRODUCTION

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Patients undergoing spine surgery in prone position are susceptible to significant haemodynamic changes.(1,2) Spine surgery presents a number of unique challenges to the anaesthesiologist.(3,4) The emphasis remains on the provision of good operative conditions by providing haemodynamic stability, minimum interference with the neurological monitoring, and good pain relief with multimodal analgesic techniques. These techniques help for a rapid high-quality recovery and early assessment of neurological function.

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ABSTRACT

TITLE OF STUDY: A double blinded randomized control trial to comparing the efficacy of oral clonidine premedication with thedexmedetomidine infusion in the perioperative period, on anaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinalfusion.

DEPARTMENT: Anaesthesia

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DEGREE AND SUBJECT: M.D.Anaesthesiology

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OBJECTIVES:

To compare the efficacy of oral clonidine premedication with dexmedetomidine infusion in the perioperative period,onanaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion.

METHODS:

Seventyeligible patients undergoing two or more level of spinal instrumented fusion (thoracic and lumbar) under general anaesthesiawere randomly assigned to receive either oral clonidine (200 µg) as premedication and a bolus of 0.9% normal saline 10 min before induction

followed by an infusion of 0.9% saline in a predetermined volume (GroupA) during the intra operative period or placebo tablet as premedication and injection of dexmedetomidine(1µg/kg bolus) over 10 mins before induction followed by an infusion (0.5 µg/kg/hr) during the intraoperative period (Group B) till the skin closure. Standard anaesthesia protocols for induction and maintenance was followed for all. The anaesthetic concentration was titrated to keep the BIS between40-60. Morphine 0.1 mg/kg and 1 gm of i.vparacetamolwas givenfor analgesia. Intra operative hypertensive responses were treated with bolus dose of fentanyl (0.5µg/kg) and propofol (0.5 mg/kg). Intra operative hypotension was treated with either ephedrine (5mg bolus) or phenylephrine (50 -100µg) bolus. Variables such as heart rate, blood pressure, end tidal concentration and minimum alveolar concentration of isoflurane are noted every 15 min till the end of skin closure. The total dose of propofol and fentanyl used, time of stopping the study drug, time taken for recovery from anaesthesiawere also noted.

The variables were analyzed using descriptive statistical methods, means, standard deviation and frequency.The outcome variables were compared between the two groups using the independent 2 sample t – test. Discrete variables were analyzed using Chi –square test for significance. All statistical analysis was done using SPSS version 16.

RESULTS: Demographic data like age, sex, weight, duration of surgery were comparable between two groups. Both clonidine and dexmedetomidine reduces the endtidal concentration of Isoflurane but the dexmedetomidine reduces more significantly compared to clonidine at 30 min, at 1 hr and 2 hrs after proning (p value 0.03,0.001,0.06 respectively). There was no significant difference in heart rate between two groups after the study bolus till the end of surgery. Systolic and diastolic and mean blood pressure dropped significantly at the time of

proning and 5 mins after proning in the dexmedetomidine group compared to clonidine group. P value at proning -

(SBP/DBP/MBP- 0.005/0.07/0.02) P value at 5 min after proning – (SBP/DBP/MBP – 0.008/0.02/0.02)

CONCLUSION: Both clonidine and dexmedetomidine reduces the endtidal concentration of Isoflurane but the dexmedetomidine reduces more significantly compared to clonidine during surgery.Intraoperative propofoland analgesic requirement was same between both the groups.Both drugs are equally effective for controlling heart rate and for providing the controlled hypotension. Recovery time was not delayed in both the groups.

Hypotension, Hypertensive, Bradycardiaepisodes were comparable in both the groups.

INTRODUCTION

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Patients undergoing spine surgery in prone position are susceptible to significant haemodynamic changes.(1,2) Spine surgery presents a number of unique challenges to the anaesthesiologist.(3,4) The emphasis remains on the provision of good operative conditions by providing haemodynamic stability, minimum interference with the neurological monitoring, and good pain relief with multimodal analgesic techniques. These techniques help for a rapid high-quality recovery and early assessment of neurological function.

These spine surgeries are lengthy and associated with significant hypertensive response which intern increase the intraoperative blood loss.(5) They require larger dose of opioids and higher concentration of anaesthetic agents to suppress the hypertensive response which can interfere with neuro monitoring. Also these patients are on chronic pain on preoperative opioids, NSAID, acetaminophen. So it is very important to provide opioid-sparing or opioid-protective anesthesia techniques to avoid iatrogenic increase in the intensity of postoperative pain. Multi modal analgesic techniques are used to avoid the opioid induced side effects (respiratory depression, PONV, opioid induced hyper-algesia) and for the faster recovery .Combination of strong opioids with non-opioid analgesics (for instance, non-steroidalanti-inflammatory drugs, acetaminophen, ketamine) have become popular in

anesthesia.(6) Recently there has been a great interest in use of perioperative systemic α 2 agonists to decrease the peri-operative opioid consumption, pain intensity, and nausea. There have been various studies on clonidine or Dexmedetomidine and its effects on anesthetic requirement, haemodynamics and intra operative and post- operative opioid requirement comparing with placebo. There was no study comparing the effect of clonidine as premedication vs i.v Dexmedetomidine in the intraoperative period, on the anaesthetic requirement, haemodynamics and recovery from anesthesia. We conducted a randomized clinical trial comparing the oral clonidine premedication vs i.v Dexmedetomidine in the pre and intraoperative period, on the anaesthetic requirement, haemodynamic response to intubation, surgical incision and during surgery also the time to recovery from anesthesia. Also we compared the adverse events like hypotension, bradycardia between the two groups. Also the intraoperative blood loss wascompared between the two groups.

AIMS & OBJECTIVES

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Aim of the study

To compare the effects of oral clonidine as premedication Vsdexmedetomidine infusion in the intraoperative period, in patients undergoing instrumented spinal fusion.

Objective of the Study

1. To compare the effects of oral clonidine premedication Vs.i.vdexmedetomidine infusion in the intraoperative period on the anesthetic requirement, haemodynamic response to intubation, surgical incision and during surgery, also the recovery time from anesthesia in patients undergoing spine surgery with instrumented fusion.

2. To compare the intraoperative analgesic requirement between the two drugs.

3. To compare the adverse events like hypotension, hypertension and bradycardia between the two groups.

4. To compare the blood loss between the two groups.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

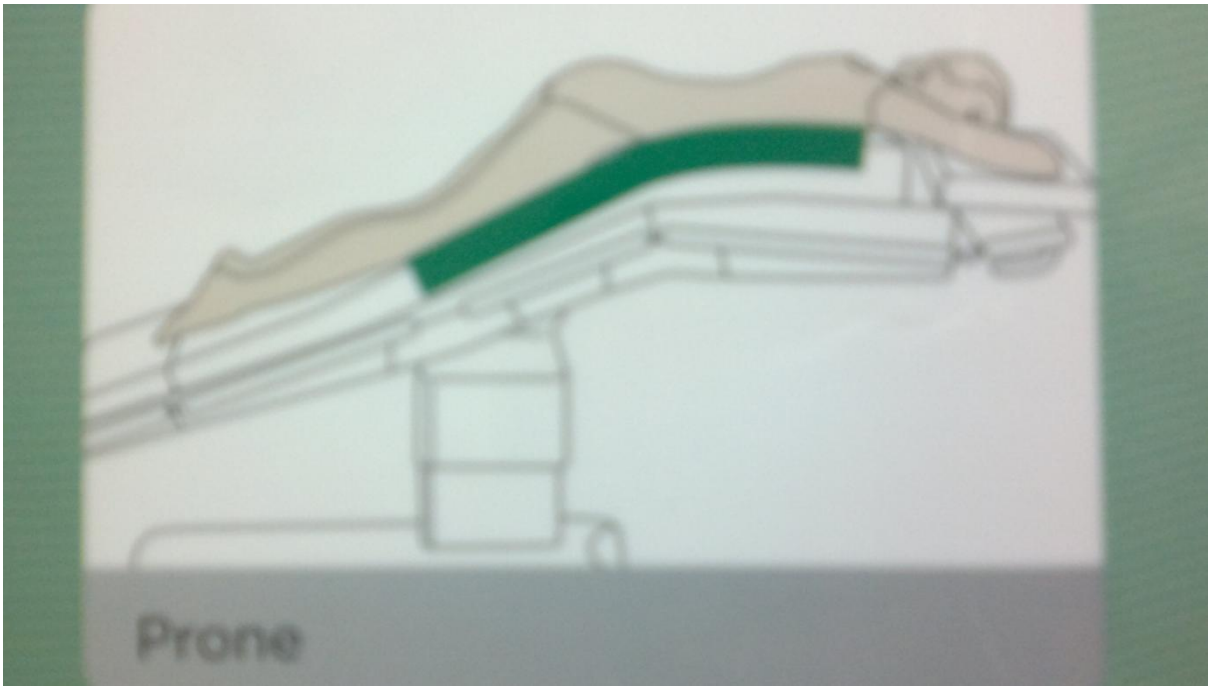
Spine surgery in prone position:

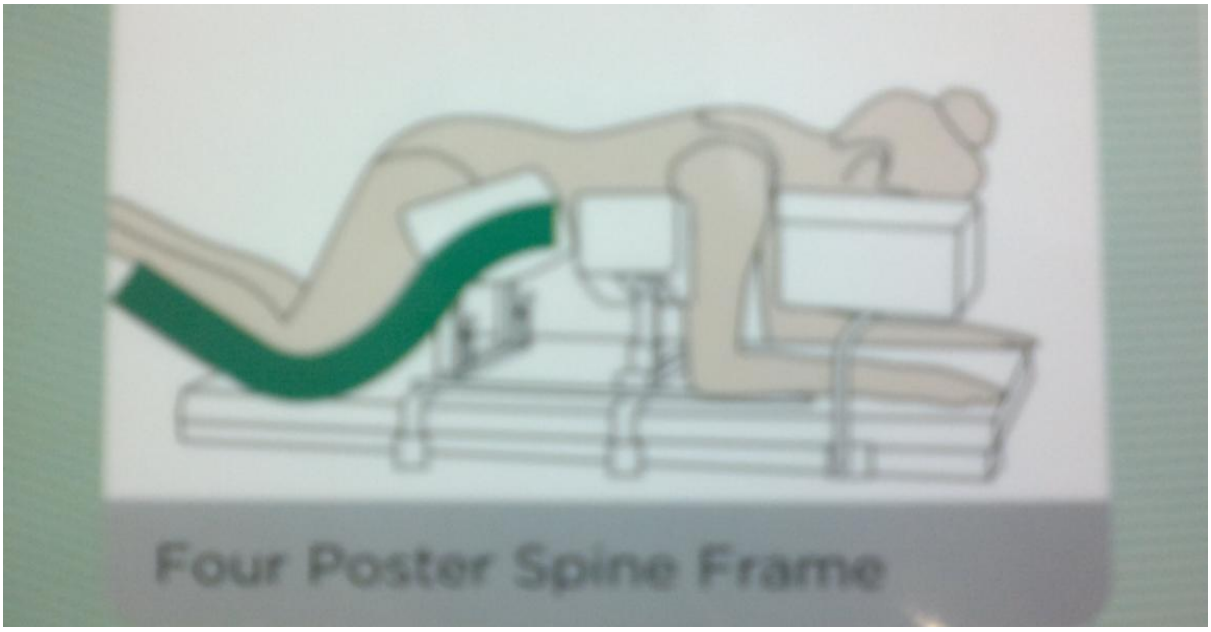
Patients undergoing spine surgery in prone position are susceptible to significant haemodynamicchanges(7). Anaesthetic considerations for spinal surgery include airway management, proper positioning to avoid positioning related nerve injury, adopting techniques to minimize the blood loss(8), techniques which allow for adequate intraoperative neurophysiological monitoring, rapid recoveryto assess the neurological status and to provide adequate post- operative analgesia(9). The emphasis remains on the provision of good operative conditions, assessment and preservation of neurological function and a rapid high-quality recovery.

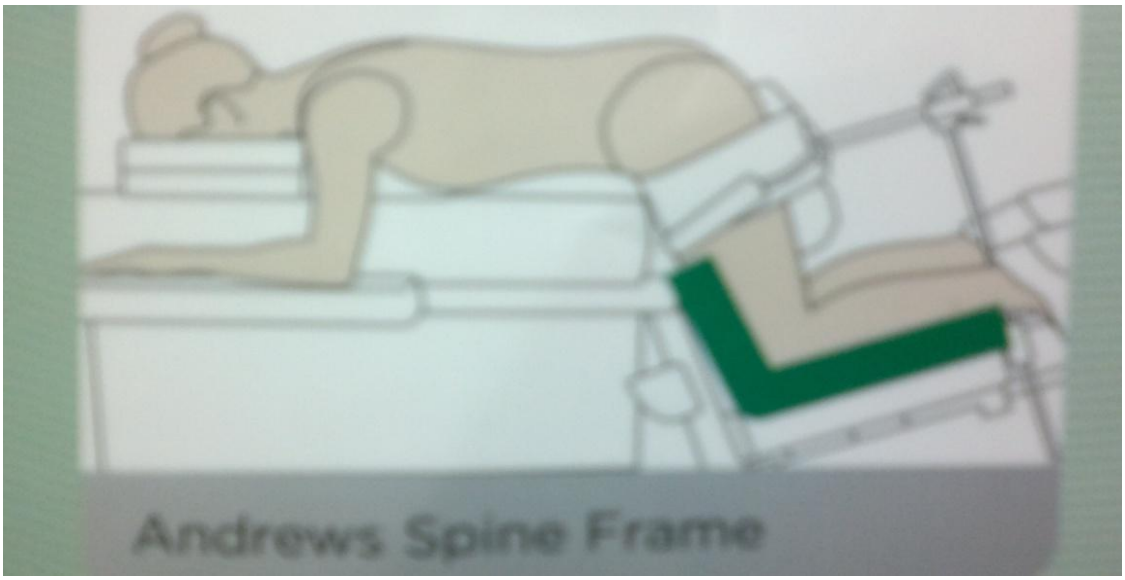
Low blood pressure, or hypotension, occurs when blood pressure during and after each heartbeat is much lower than usual. This means the heart, brain, and other parts of the body do not get enough blood.(10) Hypotensive episodes are common during anaesthesia, and controlled hypotension was once even a popular technique for reducing blood loss during surgery. However, because of the unpredictability of cerebral and other organ damage resulting from hypotension, most modern anaesthesiologists employ controlled hypotension very sparingly, or not at all. Conditions related to the deregulation of blood pressure (BP), such as orthostatic hypotension, have

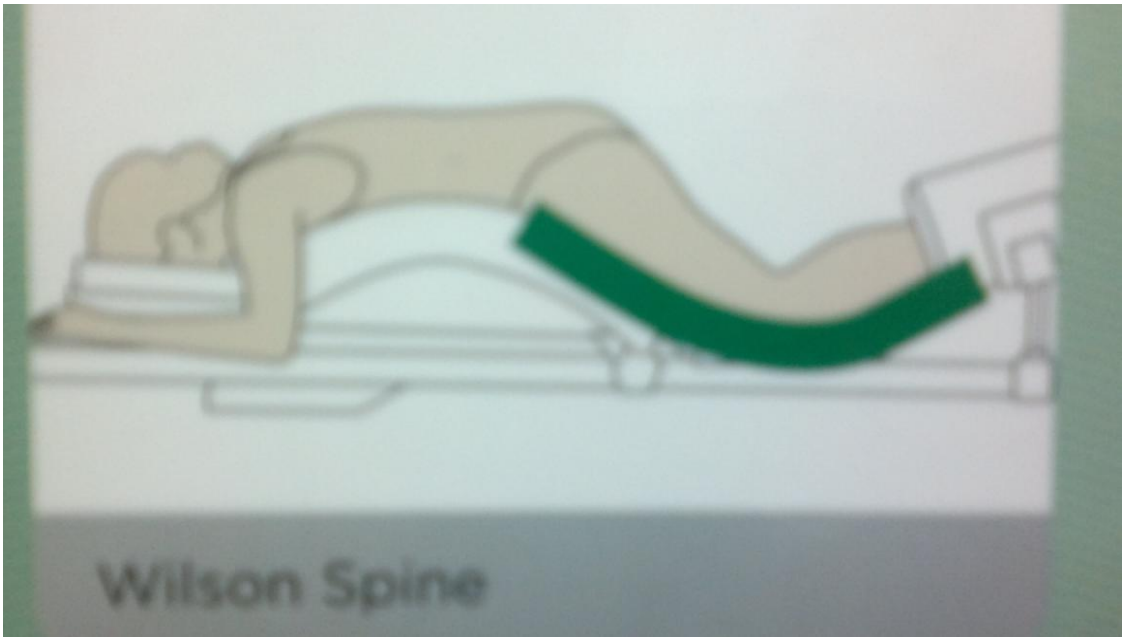
been shown to be significantly associated with cardiovascular disease (Hypertension, Ischaemic heart disease, Cardiomyopathy, etc.). Recently, the prone body position has been recognized as a possible postural factor leading to BP deregulation. Yasuharu Tabara et al conducted a cross-sectional study to investigate the BP response to a change in body position from supine to prone. The study subjects consisted of 271 middle-aged healthy males, randomly selected from the employees of a large manufacturing enterprise in Ehime Prefecture, Japan. Brachial blood pressure and heart rate were measured in sitting, supine and prone position and each difference was defined as a postural change (11). The postural changes in aortic hemodynamics were also assessed using a SphygmoCor system. The baseline BP measured in the sitting position was significantly decreased in the supine position (132±18 to 130±17 mmHg, $p<0.001$). A further reduction was observed after the postural change from supine to prone (130±17 to 125±16 mmHg, $p<0.001$). The heart rate was increased with the supine-to-prone postural change (4.1±5.8 beats/min, $p<0.001$), while it showed a significant decrease with the sitting-to-supine postural change (-7.6±5.6 beats/min, $p<0.05$). The impact of BP reduction was more prominent in the aortic artery than the brachial artery. Analysis showed that basal systolic BP was the sole significant determinant of the prone-hypotension ($p<0.001$). In conclusion, these results indicate that lying in a

prone posture could lead to unregulated postural hypotension, which has the possibility of being a novel predictor of cardiovascular fragility.




Four Poster Spine Frame


Andrews Spine Frame



Spine surgeries are very painful and also associated with significant haemodynamicpressor response. Usually these patients need a huge dose of higher concentration of anaesthetic agents. Higher concentration of anaesthetics will affect the neurological monitoring also prolongs the anaesthesiarecovery(12). High dose of opioids are associated with respiratory complication. Anaesthetic adjuncts like alpha 2 agonist will reduce the anaesthetic concentration thereby allow adequate neuro-monitoring also reduce the opioid requirement and its side effects.

Use of alpha 2 agonist in the perioperative period has been there since 1970's, as premedication and as an adjunct to anesthetic drugs. It is used

because of its sedative, anxiolytic, analgesic and its opioid sparing effect. Clonidine was the commonly used drug for this purpose(15,16). Recently Dexmedetomidine, a newer alpha 2 agonist is getting popular in anesthesia practice because of its more selective alpha 2 agonistic action compared to clonidine.(19)

Spine instrumentation is always associated with significant blood losses. Multiple factors have been suggested to influence the magnitude of this blood loss, which include surgical technique, operative time, number of vertebral levels fused, anesthetics, mean arterial blood pressure, platelet abnormalities, dilutional coagulopathy, and primary fibrinolysis.

Blood-sparing techniques can be divided into two groups, based on their goals: they are aimed at decreasing the bleeding itself (e.g., controlled hypotension, local vasoconstrictors, epidural blockade) or with chemical/biological agents (e.g., desmopressin,aprotinin, tranexamic acid, epsilon-aminocaproic acid, estrogens, bone wax, hemostatic “sponges,” fibrin sealants)] or at decreasing the need for homologous transfusion(e.g., acute haemodilution, planned autologous transfusion, cell-saving systems, erythropoietin).

Controlled hypotension

Controlled hypotension is defined as a reduction of the systolic blood pressure to 80-90 mm Hg, a reduction of mean arterial pressure (MAP) to 50-65 mm Hg or a 30% reduction of baseline MAP. Pharmacological agents used for controlled hypotension include those agents that can be used successfully alone and those that are used adjunctively to limit dosage requirements and, therefore, the adverse effects of the other agents.

The characteristics of an ideal hypotensive agent include easy administration, predictabilitywith anaesthetic agents, and lack of side effect while maintaining adequate perfusion of the vital organs.

Agents used successfully alone include inhalation anaesthetics, sodium nitroprusside, nitroglycerin, trimethaphancamsilate, alprostadil (prostaglandin E1), adenosine, remifentanil. Agents that can be used alone or in combination include calcium channel antagonists (e.g. nicardipine), beta-adrenoceptor antagonists (beta-blockers) [e.g. metaprolol, esmolol].Alpha-2 adrenergic agonists (clonidine and Dexmedetomidine) have been used successfully as adjuvants, oral premedication and intravenous infusion during anesthesia to induce controlled hypotension.

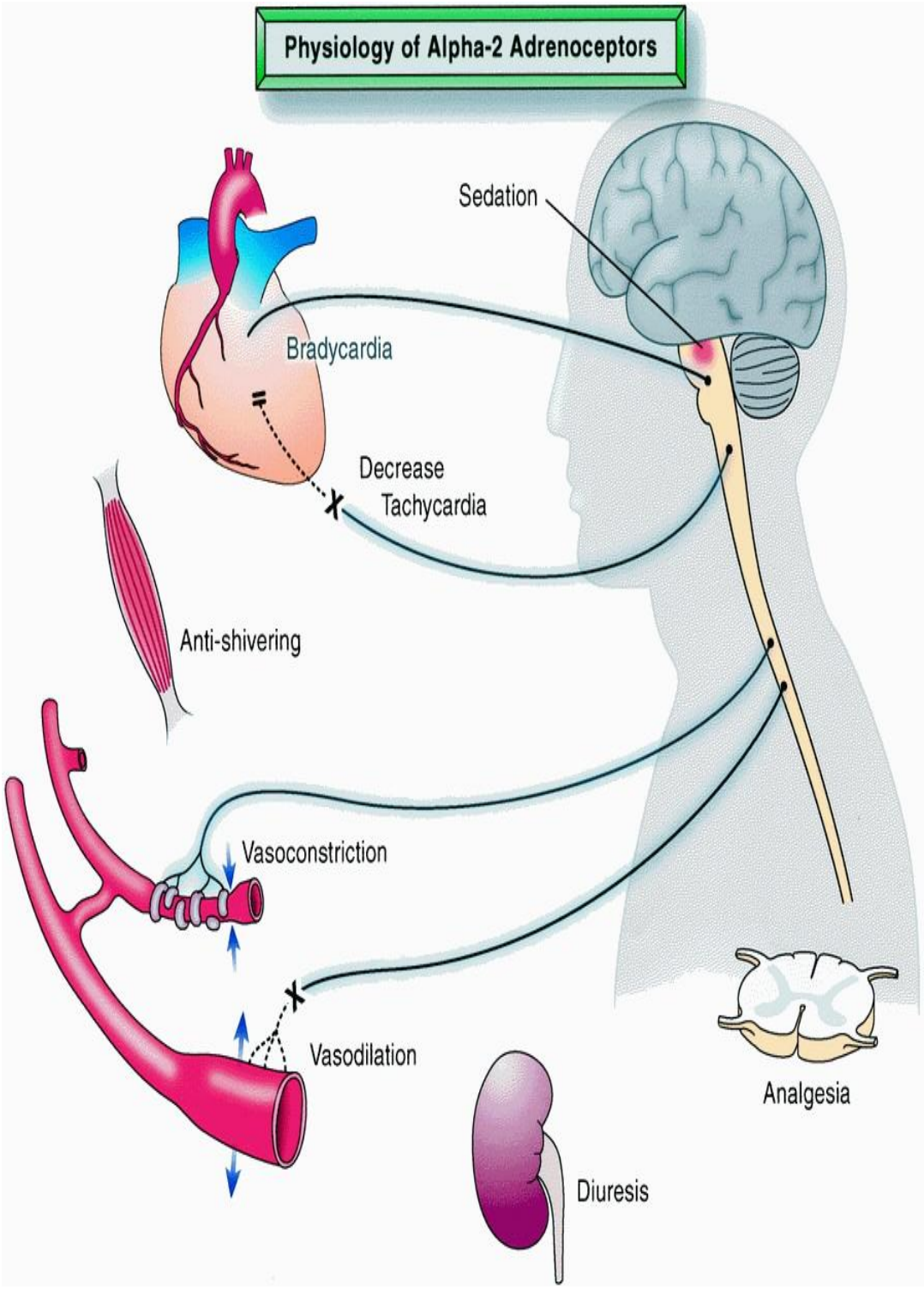
Physiology of adrenoreceptors

The adrenergic receptors are a class of G protein-coupled receptors that are targets of the catecholamine, especially norepinephrine and epinephrine. Raymond Ahlquist, Professor of Pharmacology in Georgia, US was the first one who differentiated adrenergic receptors into alpha and beta based on responses of various amines in different physiological preparations (1948) (16). Further research on this led to sub-classification of adrenoreceptors based on their synaptic locations. Alpha receptors have the subtypes alpha 1($\alpha_{1)}$ (a G_q coupled receptor) and alpha α_2 (a G_i coupled receptor). Beta (β) receptors have the subtypes like β_1, β_2 and β_3. All three are linked to G_s proteins.

Functionally alpha 1 adrenoreceptors were found to be excitatory and alpha 2 receptors found to be inhibitory and excitatory. Further work lead to discovery of three alpha 2 iso-receptors namely alpha 2a, 2b and 2c,which were presynaptic, postsynaptic and extra synaptic.(17) Similarly alpha1 adrenoreceptors are further classified in to alpha 1a, 1b and 1d.

Distribution of alpha-2 adrenoreceptors

The medullary dorsal motor complex in the brain stem has a high density of alpha2 adrenoceptors. Activation of alpha 2 receptors at this site is responsible for the haemodynamic response seen with this group of drugs. The locus coeruleus is the largest noradrenergic cell group in the brain and being an important modulator of wakefulness, it is the major site for sedative hypnotic action of alpha 2adrenoceptor agonists. The vagusnerve,as well as the intermediolateral cell column, substantiagelatinosaand dorsal horn of the spinal cord (18) have high density of alpha 2adrenoceptors.


Physiology of Alpha-2 Adrenoceptors
Sedation
Bradycardia
Decrease
Tachycardia
Anti-shivering
Vasoconstriction
Vasodilation
Analgesia
Diuresis

Physiological effects of alpha 2 stimulation and their clinical implications at various system

Respiratory System:

Alpha 2 agonists have minimal effects on ventilation in therapeutic doses.(3) They do not affect hypoxic or hypercapnicventilatory drive. Do not potentiate the effect of opioid induced respiratory depression.(19)

Cardiovascular system:

The alpha 2a adrenoreceptors are primarily distributed in the periphery, whereas alpha 2b, 2c are in the brain and spinal cord respectively. Postsynaptic alpha 2adrenoreceptors are located in peripheral blood vessels and its stimulation by an agonist produce vasoconstriction, whereas agonist acts on the presynaptic alpha2 adrenoreceptors inhibit the release ofnorepinephrine causes vasodilatation and decrease in heart rate.(20) Protective reflexes triggered by reduction of blood pressure are largely functional despite administration of alpha 2 agonists as they do not alter catecholamine metabolism or block adrenergic receptors.(21)

Central nervous system :

Stimulation of alpha 2 receptor by the agonist at locus ceruleus reduces the neuronal firing cause sedation and hypnosis. Stimulation of the alpha 2 receptor at the dorsal motor nucleus of the medulla causes bradycardia and hypotension and stimulation of this receptor at the intermediolateral cell column and substantiagelatinosa of the spinal cord results in inhibition ofreleaseof the nociceptive mediator (the substance P) is responsible for its analgesic effect. Alpha 2 agonist action on cerebral vasculature leads to cerebral vasoconstrictionand decrease in cerebral blood flow.(22)

Other physiological effects of alpha 2 receptor stimulation:

- Diuresis due to inhibition of antidiuretic hormone release and antagonism ofantidiuretic hormone tubular effects.

- Decongestant and anti-sialogogue effects.

- Affects the insulin release (clinically not significant).

- Decreases the adipose tissue lipolysis and increases the growth hormone secretion.

Commonly used alpha 2 adrenergic receptor agonists in the clinical practice:

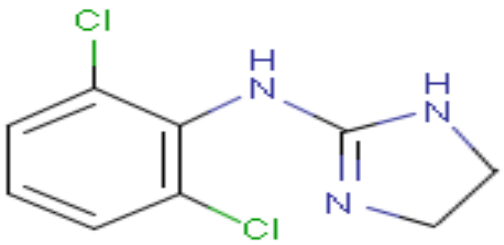
1. Clonidine

2. Dexmedetomidine

Clonidine

Clonidine hydrochloride is an imidazole derivative. It was synthesized in early 60s, as a derivative of the known alpha sympathomimetic drug naphazoline and tolazoline. It was originally developed as a nasal vasoconstrictor. During clinical trial, it was found to cause hypotension, sedation and bradycardia. It was introduced in 1966 as a first antihypertensive known to act on the CNS.

Chemical Formula : 2[(2, 6 Dichlorophenyl) Imino] Imidazoline Mono hydrochloride



Clonidine

ChemicalStucture:

Dose **Range**: Clonidine has been used in a wide dose range for various studies. The clinically effective range is 2 to 7 μg/kg body weight.

Pharmacokinetics:

Clonidine is rapidly and almost completely absorbed from gastrointestinal tract with bioavailability of 100%. After oral intake, onset of action starts within 30-60 minutes and peak plasma concentration is reached within 90 min. The elimination half-life ranges between 6-24 hours with a mean of about 12 hours.

Clonidine can be administered intramuscular, intravenous, transdermal, by nebulisation, extradural and intra-thecal routes. Rectal administration is known in children. It is well absorbed through skin because of its low molecular weight and high lipid solubility. After transdermal clonidine patch implantation, stable plasma concentrations are reached after 2-3 days. Clonidine is distributed throughout the body, the highest concentration being in organs of elimination i.e., kidney, gut and liver. The brain concentrations are low but higher than plasma concentrations.

Clonidine is metabolised mainly by the liver to produce P-Hydroxyclonidine which subsequently undergoes glucuronidations to produce O-glucuronide

and is excreted in urine. 40 to 60 % of an orally administered dose is excreted unchanged in urine within 24 hours. 95 % of clonidine administered is excreted in urine and faeces in 72 hours and complete clearance occurs in 5 days.

Uses of clonidine:

a) As a premedicant - becauseof its sedative,anxiolytic,analgesic, and opioid sparing effect also it decreases the anaesthetic requirement.

Chandrasekaraiah et al, in their study have shown that oral premedication with 150 mcg clonidine effectively counteracted the cardiovascular changes induced bypneumoperitoneum in patients undergoing elective laparoscopic cholecystectomy.(23)

Study done by **Kalajdzija et al** in elective non-cardio surgical population, observed that patients who had clonidine at the rate of 0.2 µg/kg/min 30 min prior to start of surgery had considerably less stress response, which was shown through variation of cortisol levels during operation, glycemic levels and vital parameters.(24)

Poutlu et al observed that the haemodynamic response to intubation was lower in clonidine premedicated patients (4.5 µg/kg) undergoing breast surgery.(25)

Marchal et al in their study has proved that 300 µg of clonidine premedication reduced the isoflurane and fentanyl and urapidil requirement during ENT surgery, also it has reduced the haemodynamic response to intubation and the surgical bleeding.(26)

Friedberg et al in their study comparedthe propofol consumption rates in patients undergoing office based surgical procedure under BIS guided propofol-ketamine anesthesia with or without clonidine premedication (200µg) and observed that oral clonidine premedication reduced propofol requirements.(27)

b)For controlled hypotension in reduction of surgical bleeding.

Woodcock TE et al, in their study, observed that, the patients who underwent middle ear or nasal surgery with single dose oral clonidine premedication required lesser mean inspired isoflurane concentration to induce hypotension.(28)

In a double- blinded, randomized clinical trial, **Anvari et al** evaluated the effect of oral clonidine premedication on blood loss in lumbar spine fusion surgery under anaesthesia with propofol and remifentanil and concluded that clonidine could reduce surgical blood loss even at the same levels of mean arterial pressure with control group.(29)

Ebnesshahidi et al , in their study on patients who underwent caesarean section under general anaesthesia with clonidine premedication had better hemodynamic profile and lesser bleeding during the intraoperative period. (30)

Dexmedetomidine

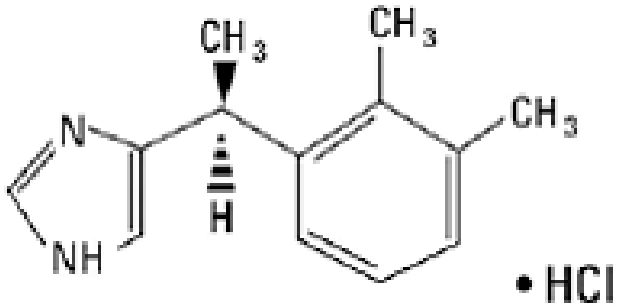
Pharmacology of Dexmedetomidine

Dexmedetomidine is an imidazole compound and is an active-isomer of medetomidine. It has an imidazole chain in its structure which is common to other alpha 2 adrenoceptor agonists. Dexmedetomidine was approved for human use in 1999 by the Food and Drug Administration. It was initially approved for sedation ofintubated and mechanicallyventilated patients in the intensive care setting for up to 24 hours. It wasintroduced in anaesthetic practice for sedation during procedures in 2008.

ChemicalFormula:

(+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride.

Chemical structure:



Dose Range: 1µg/kg as a bolus followed by 0.2-07 µg /kg/ hr. as an infusion.

Mechanism of action of Dexmedetomidine

The mechanism of action of Dexmedetomidine is unique and differs from the currently used sedative drugs. Alpha2-adrenoceptors are found in many sites, the Locus Ceruleus being, the predominant noradrenergic nuclei of the brainstem. Presynaptic activation of the alpha2-A adrenoceptor in the Locus Ceruleus inhibits the release of norepinephrine (NE) resulting in the sedative and hypnotic effects and modulates nociceptive neurotransmission leading to analgesia. Postsynaptic activation of alpha2-adrenoceptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia. Also, activation of the alpha2-adrenoceptors in the CNS results in an augmentation of cardiac vagal activity. Combined, these effects can

produce analgesia, sedation and anxiolysis. At the spinal cord, stimulation of alpha2-receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of the release of substance P.

Pharmacokinetics:

Dexmedetomidine has a rapidredistribution half-life of6 minutes. It has volumeofdistribution of 118 litres.(31) It is highly protein bound (94%). The elimination half- life 1.5 to 3 hours following intravenous or intramuscularinjection. But it takes longer about 5-6 hours after transdermal application.(28)

Dexmedetomidine demonstrates linear concentration dependent kinetics when given as an infusion.(28) Bioavailability is more following transdermal administration as compared to intramuscular route, 88% and 73% respectively.(32) Dexmedetomidine is metabolized in the liver. It undergoes complete hydroxylationthrough direct glucuronidation and cytochrome P450 metabolism in liver and it isexcreted by kidneys as methyl and glucoronide conjugates.(30) Renal excretion is95% and faeces 4%. There are no active metabolites.

Pharmacodynamics:

Following a loading dose, peak sedative effects occurs in 25 minutes.A biphasic cardiovascular response has been observed after the administration of Dexmedetomidine. An intravenous bolus of 1 mcg/kg of Dexmedetomidine initially results in a transient increase of the blood pressure due to alpha 1 receptor stimulation, a reflex fall in heart rate (especially in younger, healthy patients) and followed by a decrease in blood pressure due to the inhibition of the central sympathetic outflow.

Dexmedetomidine induced sleep:

Sedation due toDexmedetomidine resembles natural sleep with easy arousability. Dexmedetomidine hyperpolarizes the locus ceruleus, inhibiting the release of norepinephrine and hence produces sleep similar to that of non REM period. This differs from sleep produced by benzodiazepines or opioids. (33)

Guo et al has done a study on rats to locate the site of action of Dexmedetomidine and has demonstrated that Dexmedetomidine acts directly on the locus cerules and produce an anti-nociceptive effect which can be blocked by specific α 2antagonists. The action of Dexmedetomidine also

resulted in the increase in activation of alpha 2 adrenoceptors in the spinal cord. (34)

Side-effects

The common adverse effects of Dexmedetomidine include hypotension, hypertension, nausea, bradycardia. , Rare side effects which include various atrio-ventricular blocks and atrial fibrillation. Most of these adverse effects occur during or briefly after the bolus injection.

Uses of Dexmedetomidine in the perioperative period

a) As a premedicant due to its sedative, anxiolytic,analgesic,sympatholyticand anaesthetic sparing properties.

b) As an adjunct to general anaesthesia.

c) As a sole agent for total intravenous anaesthesia.

d) Causes significant prolongation of sensory and motor blockade when usedas an adjuvant in regional anaesthesia.

e) As an ideal agent in monitored anaesthesia care.

f) Effective agent for controlled hypotension due to its central and peripheralsympatholysis.

The first human study by **Aho et al**, evaluated the effects of Dexmedetomidine 0.3 and 0.6 µg/kg on haemodynamic response to laryngoscopy and requirements of isoflurane for maintenance of anaesthesia in patients undergoing abdominal hysterectomy. The major findings of that study were that Dexmedetomidinepre-anaesthetic medication at a dose of 0.6 µg /kg blunted the tachycardia and hypertensive response to laryngoscopy and endotracheal intubation. It also diminished isoflurane requirements during surgery.(35)

An observational study by **Ghodki et al** on patients undergoing laparoscopic surgeries under general anesthesia with Oxygen, Nitrous oxide and Isoflurane, where 1 µg/kg bolus followed by 0.2 µg/kg/hr. infusion of Dexmedetomidine was given during the intraoperative period. The depth of anaesthesia was monitored using entropy.They have observed that there was a 62.5% reduction (0.75 mg/kg) in the induction dose of propofol, with a 30% less end-tidal concentration of isoflurane requirement for maintenance of anaesthesia.(36)

Keniya et al in their study of isoflurane-opioid-Dexmedetomidine based anaesthesia have found that the need for thiopentone and isoflurane was decreased by 30% and 32%, respectively, in the Dexmedetomidine group as compared to the control group. After tracheal intubation, maximal average increase was 8% in systolic and 11% in diastolic blood pressure in Dexmedetomidine group, as compared to 40% and 25%, respectively, in the control group. Similarly, average increase in heart rate was 7% and 21% in the Dexmedetomidine and control groups, respectively. The opioid (fentanyl) requirement during the operation was 100±10 μg in the control group and 60±10 μg in the Dexmedetomidinegroup.(37)

Khan et al has observed a dose related effect of Dexmedetomidine on MAC of isoflurane in his study. At plasma concentration of 0.35-0.75 ng/ml dexmedetomidine caused significant MAC sparing effects. Eventhough isoflurane did not appear to affect the pharmacokinetics of Dexmedetomidine.(38)

In a double- blind, placebo-controlled trial involving healthy male volunteers, the investigators found that a 2-min intravenous infusion of Dexmedetomidine produced a transient increase in mean arterial blood pressure and a longer lasting decrease inmean arterial blood pressure.(39)

In a study on healthy women scheduled for dilatation and curettage (D & C) of the uterus the authors concluded that Dexmedetomidine pre-anaesthetic medication (0.5µ/kg) decreased the thiopental anesthetic requirements by 30% and improved the recovery time from anaesthesia as measured by visual analogue scale with no serious hemodynamic or other adverse effects.(40)

In a prospective randomized study involving patients undergoing fast-track CABG, **Menda etal** has used Dexmedetomidine as an adjunct in patients undergoing myocardial revascularization receiving beta blocker treatment and observed the attenuation of hemodynamic response to endotracheal intubation.(41)

Ayoglu et al in their study determined the effectiveness of Dexmedetomidine in reducing bleeding and intraoperative opioid requirement during septoplasty surgery under general anaesthesia. (42)

Depth of anaesthesia.

Various modalities are being used to measure the depth of anaesthesia in the perioperative period. One of such monitor which has found wide application in current anaesthetic practice is Bispectral index (BIS) monitor.

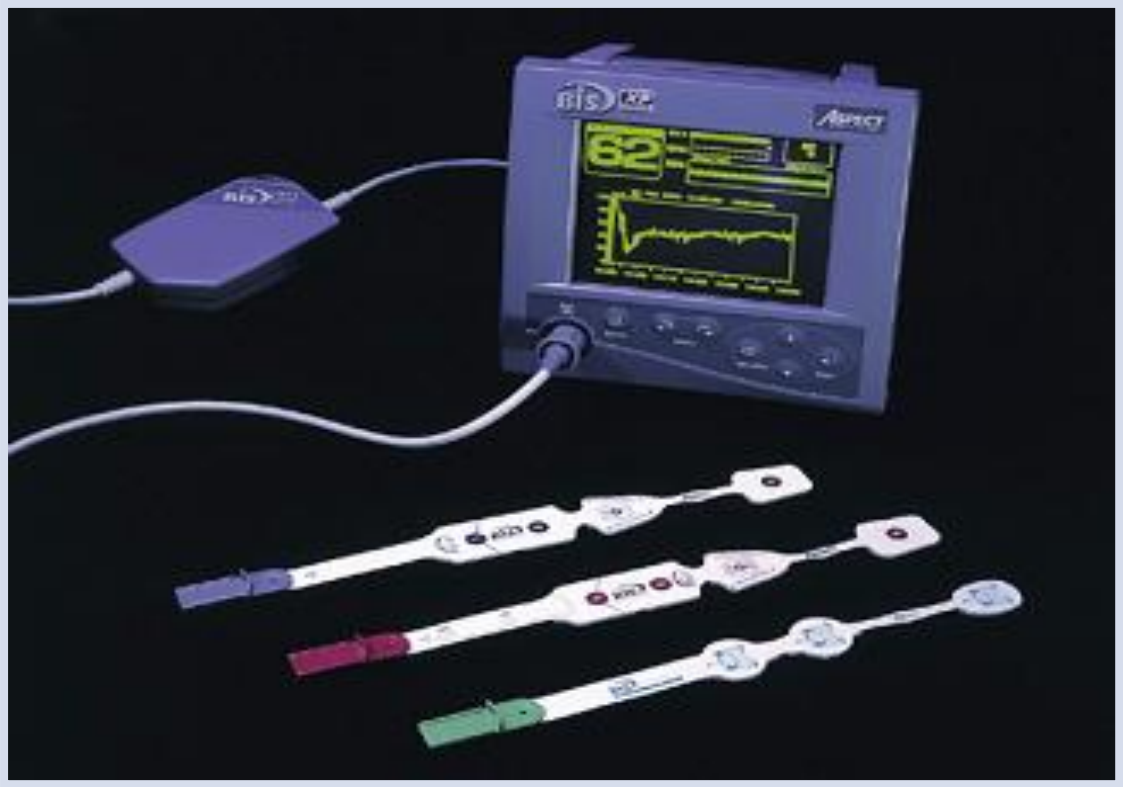
The spectral index is a statistically based, empirically derived complex parameter. It is a weighted sum of electroencephalographic sub parameters, including a time domain, frequency domain, and high order spectral sub parameters. The BIS monitor provides a single dimensionless number, which ranges from 0 (equivalent to EEG silence) to 100 (equivalent to fully awake and alert). A BIS value between 40 and 60 indicates an appropriate level for general anaesthesia.

The non-invasive sensor has self-adhesive backing, much like a typical EEG pad. The sensor then sends raw EEG information through the cable and converter to the BIS engine. This engine processes the EEG data according to an algorithm that combines select EEG features to produce a BIS index.

Glass et al had shown that the BIS corelated well with the level of responsiveness and provided an excellent prediction of the level of consciousness with propofol,midazolam and isoflurane anaesthesia.(43)

Kearse et al in his study has observed that BIS could be used to predict the hemodynamic reponse to laryngoscopy and intubation during anaesthetic induction.(44)

BIS Monitor used to assess the Depth of Anaesthesia.



MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY SETTING: The study was conducted in the Orthopaedics and Neurosurgical operating suites.

STUDY DESIGN: A double blinded randomized control trial to compare the efficacy of oral clonidine as premedication Vs Dexmedetomidine infusion in the perioperative period, on anaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion.

STUDY POPULATION:

a. Inclusion Criteria:

1. Adult ASA 1 and 2 patients between 18 to 60 yrs. undergoing elective, two or more than two levels of decompression and instrumented spinal fusion.

b. Exclusion Criteria:

1. ASA 3 and 4 patients.
2. Patients who underwent discectomy, and single level decompression and fusion.
3. Patients with creatinine more than 1.5 mg%

4. Patients with liver dysfunction

5. Patients who has known allergy to the drug.

6. Pregnancy

METHOD OF RANDOMIZATION:

A computer generated set of randomized numbers by using block randomization.

METHOD OF ALLOCATION CONCEALMENT:

Envelops specifying only the serial no was given to the anesthesiologist, who anaesthetized the patient and it was noted on the data sheet.

BLINDING AND MASKING:

Intraoperative drug administered both, bolus and infusion was prepared by the pharmacist, in our institution. Only the serial number on the envelope is noted by the anaesthesiologist who anaesthetized the patient on the Data sheet.

PRIMARY OUTCOMES: time : Intra-operative anaesthetic requirement.

S**ECONDARY OUTCOME/S**: Intraoperative haemodynamic stability, time taken for recovery (time interval between the stopping of inhalational agent till the time of extubation).

STUDY PERIOD:

The study was conducted over a period of 9 months between February and October of 2012.

TARGET SAMPLE SIZE AND RATIONALE:

The required sample size to show a difference of 0.04 in 80% of the times between Clonidine & Magnesium Sulphate, a altan et al BJA 94(4):438-41(2005) was found to be 37 in each arm with a standard deviation to be 0.06 in each group at 5% level of significance.

Formula:

$$n = \frac{\left(Z_{\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 2s^2}{d^2}$$

where, s = standard deviation

d = difference between the two drugs

A total sample size of 74 patients were needed for the study.

SELECTION OF STUDY PATIENTS:

Study was conducted after getting the approval from the institutional review board (IRB) and the ethics committee. Patients scheduled for more than two level of decompression and instrumented spinal fusion were included in the study (lumbar and thoracic). Patients who underwent single level fusion and discectomy were not included in the study. In our institution all patients undergoing surgery are seen in the pre-anaesthesia clinic by the qualified anesthesiologist and all our study patients who met the eligibility criteria were already seen and accepted for the planned surgical procedure. Those patients who met the eligibility criteria were approached by the anaesthesiologist who is involved in the study on the day before surgery and explained about the study in detail on their own language and got the consent also wrote the premedication order.

Total of 80patients were approached, out of 80 patients, 74 were recruited for the study after getting the informed consent. In 4 patients, because of violation in the study protocol during the premedication time, study was not carried out.

Eligible patients were randomly divided into two groups ,Group A and Group B

Group A - Oral clonidine (200 µg) 60-90mins prior to induction, as premedication followed by saline infusion (both bolus and infusion) in a predetermined volume during the intraoperative period till the skin closure.

Group B- Placebo tablet as premedication and injection of Dexmedetomidine 1µg/kg bolus over 10mins before induction followed by an infusion of 0.5 µg/kg/hr.

ANAESTHESIA PROTOCOL:

Premedication:

Premedication drugs were prepared by the pharmacist in an envelope and numbered serially. Patients in Group A received Tablet Clonidine 200 µg along with Tablet Perinorm 10 mg. While patients in Group B received a placebo tablet along with Tablet Perinorm 10 mg as premedication.

Pre-induction period:

Patients were identified by the nurse and attending anesthesiologist and reassessed in the preoperative holding area, brought to anaesthesia room, where peripheral i.v cannula(18 or 16G) and radial arterial line (20 G) was inserted under local anesthesia.

Once the operating room was ready, patient was brought to operating room. Standard anaesthesia monitors like NIBP, ECG, SpO2, invasive arterial line, BIS monitor were established. Baseline values were noted. Study drug was connected and the bolus dose was given over 10 minutes using the syringe pump which delivers the drug in ml/hr.

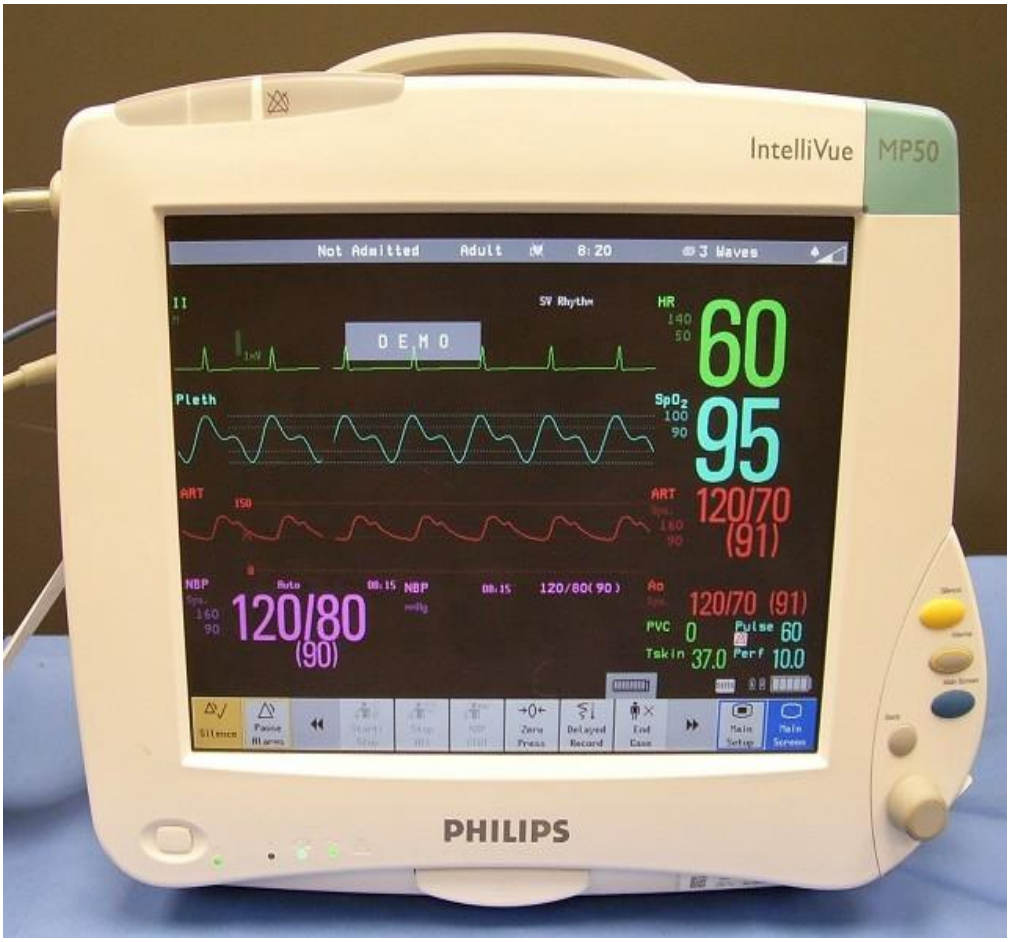
Rate of bolus infusion was calculated using the following formula and it was given over a period of 10mins.

Weight of the patient x 6 /5= (n) ml/hr. for 10mins.

Patients in Group A received 0.9% physiological saline solution while patients in Group B received 1µg/kg of Dexmedetomidine. During the start and end of bolus injection the Heart Rate, Blood Pressure (Systolic, Diastolic and Mean)and BIS values were recorded.

Syringe pumps used for the infusion of study Drug:

Monitor (Philips MP50- Intellivue) used during the study period.



Induction and Maintenance

Patients were induced with fentanyl 1 µg /kg followed by propofol 1 mg/kg then aliquots of 10 mg of propofol boluses till the BIS value drops down below 60 or till the loss of eye lash reflex. Then patients are paralyzed with vecuronium 0.1mg/kg, after 3mins of mask ventilation, patients' trachea was intubated with appropriate size ETT.Another 1 µg /kg of fentanyl was given 30 sec prior to intubation. Patients were turned prone for surgery and haemodynamic changes were noted. Anaesthesia was maintained with 50% oxygen, air and isoflurane. Isoflurane concentration was titrated to keep the BIS between 40-50. Incremental doses of i.v morphine up to 0.1mg/kg was given over a period of 30 mins after proning. Infusion of study drug was started as soon as the patient is turned prone. Volume of Infusion was calculated as follows :

Weight of the patient/ 10= (n) ml/hr. , using the same infusion pump and infusion was continued till the start of skin closure. Vecuronium was given as an infusion to maintain two twitches in TOF and stopped at the beginning of skin closure. I.V Paracetamol (1 gm.) was given prior to skin incision and it was repeated after 6 hrs. if the surgical time exceeds more than 6 hrs. Heart rate and blood pressure, end tidal isoflurane concentration and MAC of isoflurane were noted every 15 min till the skin closure. Number of episodes of hypotension and hypertension were noted during the study

period.Hypotension was defined as 10% drop from the pre induction value and hypertension was defined as 20% rise from the pre-induction value. Hypotension was treated with bolus dose of 5 mg of ephedrine if the heart rate is less than 60 or 50 -100 µg of phenylephrine bolus if heart rate is above 80. Hypertension was treated with bolus dose of 0.5 mg/kg of propofol. If the BP is not controlled with propofol, then 0.5 µg/kg of fentanyl was given.

Extubation

At the end of skin closure isoflurane was stopped and the time of stopping the isoflurane was noted. After turning supine, patients were reversed with 0.05mg/kg of neostigmine and 10 µgm./kg of glycopyrrolate. The FGF is increased to 6l/min. After establishing the extubation criteriapatients' trachea was extubated and the time of extubation was noted.Total dose of fentanyl and propofol used,Duration of surgery, blood loss during surgery were noted. Time of stopping the study drug also noted.

Statistical analysis

After collection of the necessary data, the events such as heart rate, blood pressure, anaesthetic requirements, episodes of hypertension, hypotension and bradycardia, duration of surgery, time for awakening, and blood loss between two groups were compared. The mean, standard deviation and frequency with percentages were calculated.

The statistical analysis was performed using independent sample t-TEST. P value < 0.05 was considered statistically significant. Statistical analysis was performed with STATA 11.0 software (statacorp, 4505 Lakeway Drive College Station, TX 77845, United States).

RESULTS

RESULTS

Demography:

Table 1 shows the demographic data of both the groups, Group A (clonidine premedication) and Group B (i.v Dexmedetomidine), which were well matched for age, sex, weight and duration of surgery.

Table 1: Demographic data in each group.

Character	**Group A (Clonidine premedication)**	**Group B (i.vDexmedetomidine)**
Total no of patients	37	33
Age(yrs.)	48.64±12.2	44.6±13.6
Sex(M/F)	18/19	18/15
Weight(kg)	60.21±6.7	59.39±8.13
Duration of surgery of (hrs.)	3.686±1.0973	3.370±0.9064

There is no statistically significant difference between the two groups in regards to age, sex, weight, duration of surgery.

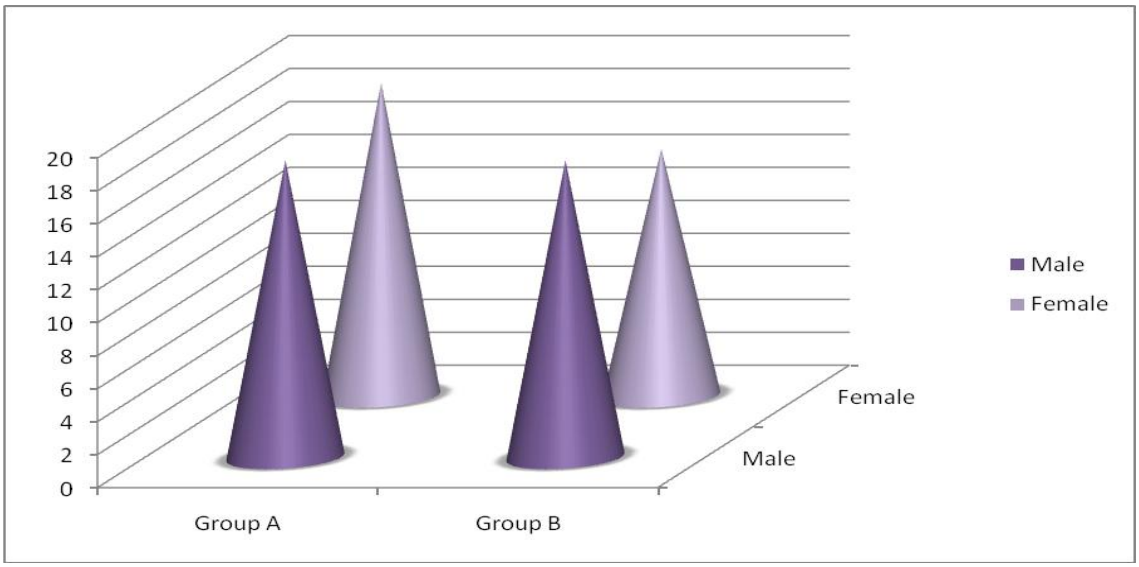
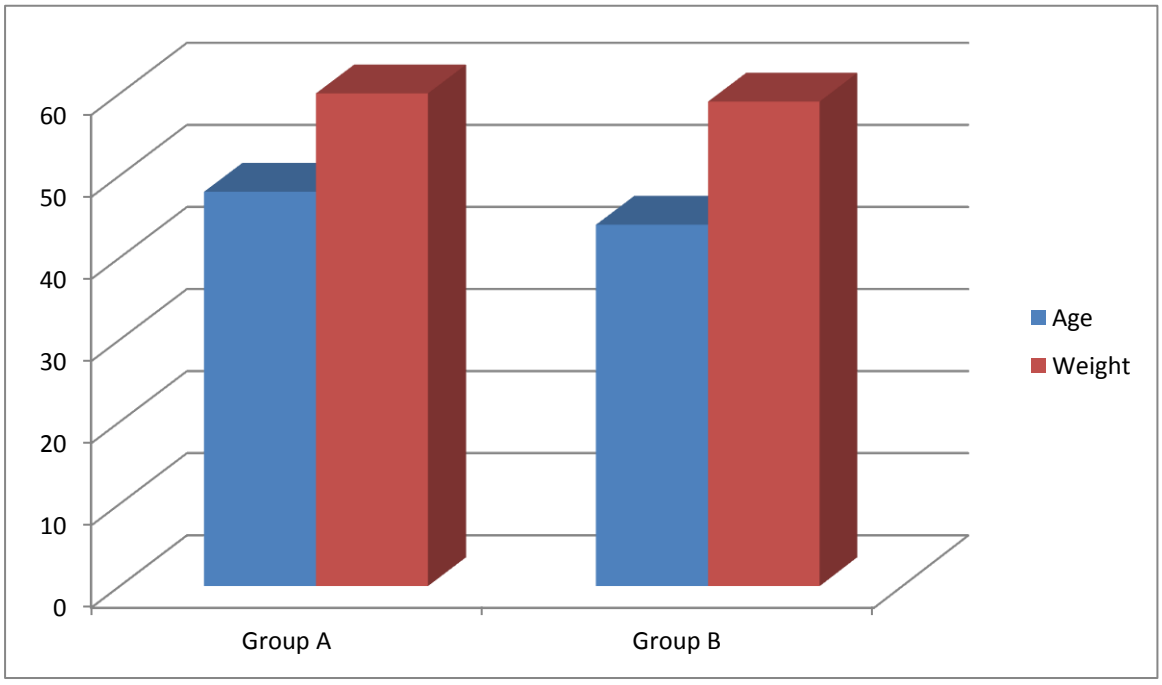


Figure 1: Demographic Data.



Heart rate

There is a significant difference in the baseline heart rates at the time of administration of the study drug bolus.Patients in Group A had lower heart rate compared to Group B(Table 2). The study drug was infused over a period of 10 minutes, A 13% decrease in heart rate was observed in the Group B (Dexmedetomidine) and 3% decrease in clonidine group at the end of study drug infusion (at 10 minutes).At induction both groups had similar heart rate (Table 2 at 10 min of Bolus). There was no statistically significant difference in heart rate response between the two groups at proning and 5, 15 min after proning also at 30 min, 1hour, 2hours, 3 hours after proning.

Demographic data like age, sex, weight were comparable between two groups. There was no statistically significant difference in heart rate response between the two groups at various time interval during the study period after the bolus injection. Both agents reduced the end tidal concentration .The end tidal concentration of isoflurane was less .

Table 2: Heart rate variation between the two groups at various time points of the study.

Heart rate	Group A Clonidine	Group B Dexmedetomidine	P – value
0min (start of study drug bolus)	80.94±14.32	89.21±19.90	0.048
10 min (end of study drug bolus)	78.37±13.11	78.45±15.05	0.982
At proning	82.62±19.94	78.18±15.98	0.311
5mins after proning	79.94±14.82	76.87±15.20	0.396
15mins after proning	74.45±11.00	73.87±14.95	0.852
30min after proning	73.89±12.41	73.57±17.83	0.931
1hr after proning	74.64±13.15	71.81±11.29	0.340
2hrs after proning	77.32±12.17	75.9±11.83	0.634
3hrs after proning	79.44±10.55	77.17±11.54	0.462

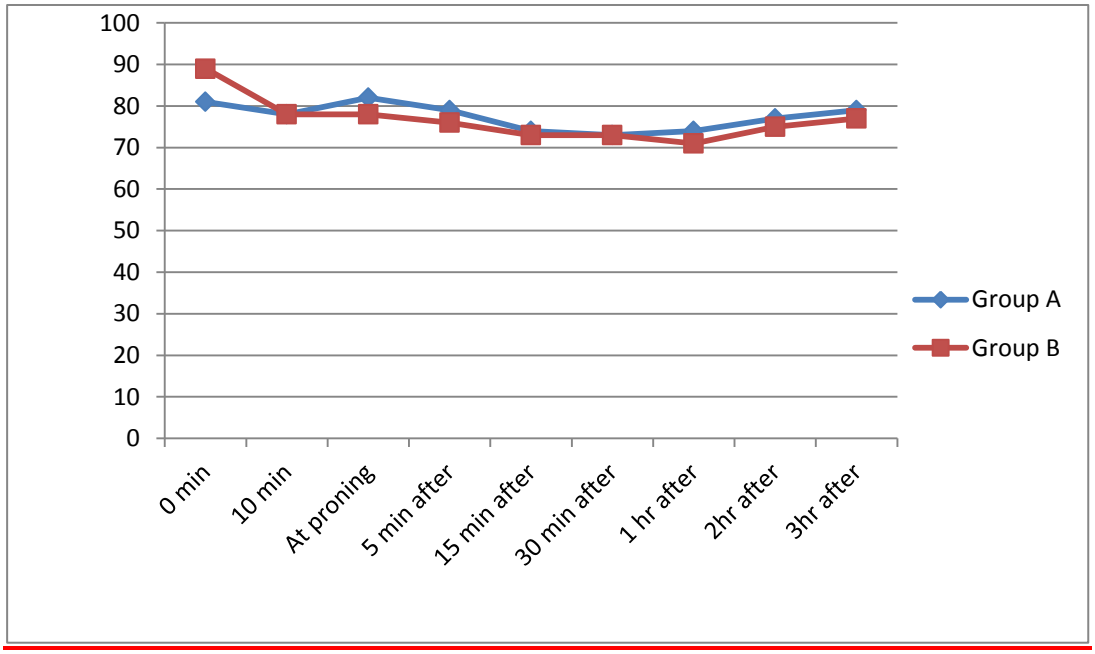


Figure 2:Heart rate variation between the two groups at various time points

Systolic Blood Pressure

There was no significant differencebetween both the groups insystolic blood pressure at the start of bolus study drug infusion.At the end of bolus study drug there was 13% decrease in systolic BPin Group B (Dexmedetomidine) compared to 11 %decrease in Group A (Clonidine), which is not statistically significant (Table 3).Both the groups had drop in systolic blood pressure after proning compared to the supine value. Patients in

Group B had more drop in BP during the bolus infusion, at proning and 5, 30 min after proning compared to Group A. At proning, the SBPdrop was 20% in Group A and 30% in Group B at proning which was statistically significant (P value 0.005).Also the 5 min value after proning was statistically significant with the p value of 0.008. Though the 30 min value after proning was lower in Group B compared to Group A, it was not statistically significant.

Table3: Systolic Blood Pressure variation between the two groups at various time points of the study.

SBP at	Group A Clonidine	Group B Dexmedetomidine	P Value
0min (start of study drug bolus)	128.51±16.80	124.12±14.18	0.573
At 10 min (end of study drug bolus)	115.62±26.85	109.09±24.74	0.295
At proning	102.67±22.77	89.51±14.11	0.005
5min after proning	102.70±21.15	91.09±13.00	0.008
15min after proning	103.56±20.21	98.03±13.49	0.187
30min after proning	99.21±19.21	97.48±13.42	0.667
1hr after proning	98.56±19.30	95.33±13.68	0.426
2hrs after proning	98.91±17.37	99.28±18.24	0.933
3hrs after proning	102.89±19.58	94.21±14.00	0.079

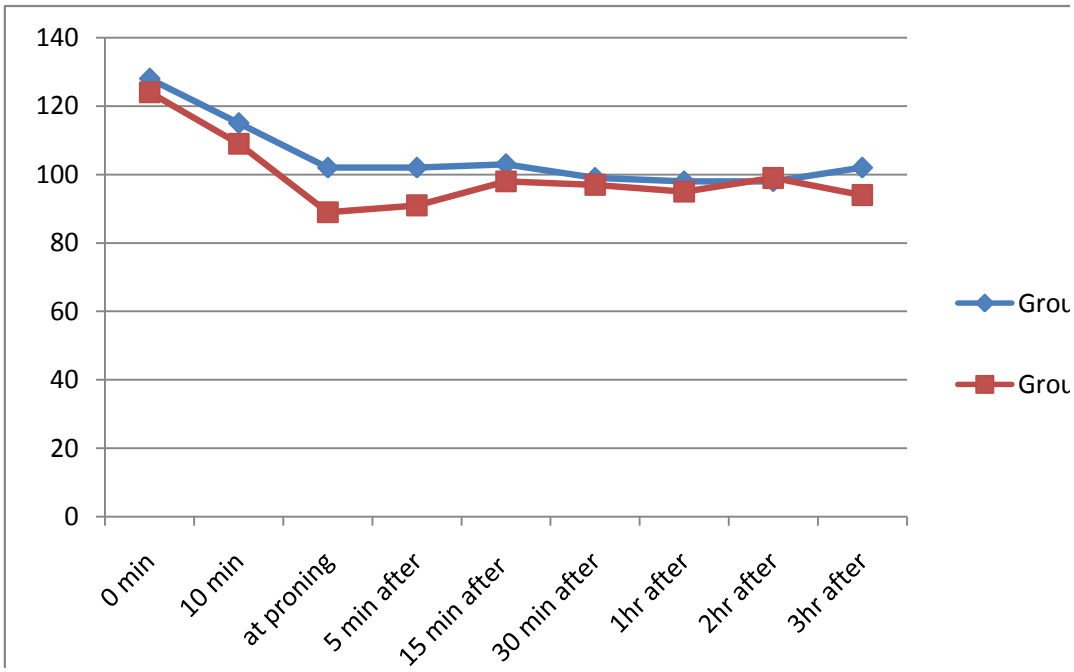


Figure 3: Sytolic pressure variation between two groups at various time points

DIASTOLIC BLOOD PRESSURE (DBP)

There was no significant differencebetween both the groups in diastolic blood pressure at the start of bolus study drug infusion. At the end of bolus study drug there was 13% decrease in DBP in Group B (Dexmedetomidine) compared to 9 %decrease in Group A (Clonidine). (Table 4) which was not statistically significant. Both the groups had drop in DBP after proning compared to the supine value. Patients in Group B had more drop in DBP at 5mins after proning compared to Group A. At 5mins after proning, the DBPdrop was 29% in Group B (Dexmedetomidine group) and 21% decrease

in Group A (clonidine group) from the baseline, which was statistically significant with a P value of 0.02.

Table 4: Variation in DBP at various time points during the study period.

Diastolic BP	Group A Clonidine	Group B Dexmedetomidine	P Value
0 min (start of study Drug bolus)	70.27±9.43	71.48±12.10	0.639
At 10 min (end of study drug bolus)	64.97±16.52	62.48±14.89	0.514
At proning	59.81±15.93	53.69±11.54	0.073
5mins after proning	59.48±12.82	53.03±1.32	0.0297
15mins after proning	59±10.32	59±10.17	1.000
30mins after proning	56±9.64	59.39±10.22	0.157
1hr after proning	56.02±10.77	58.18±9.29	0.376
2hrs after proning	58.24±10.00	58.68±10.87	0.860
3hrs after proning	56.72±9.98	57.73±10.72	0.726

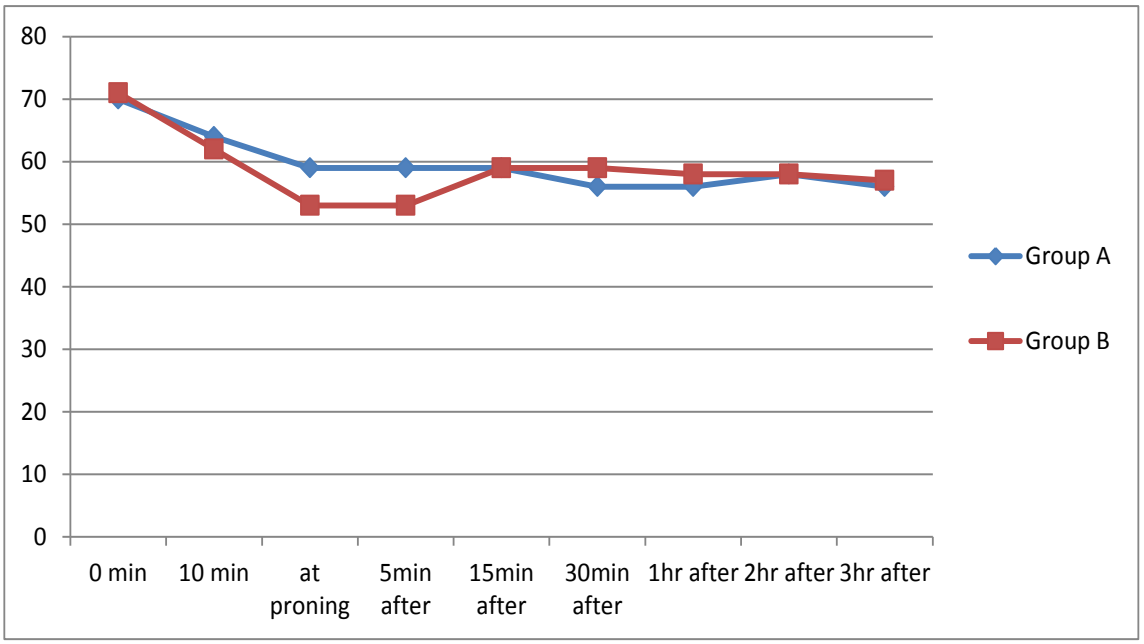


Figure 4: Variation in DBP at various time points during the study period.

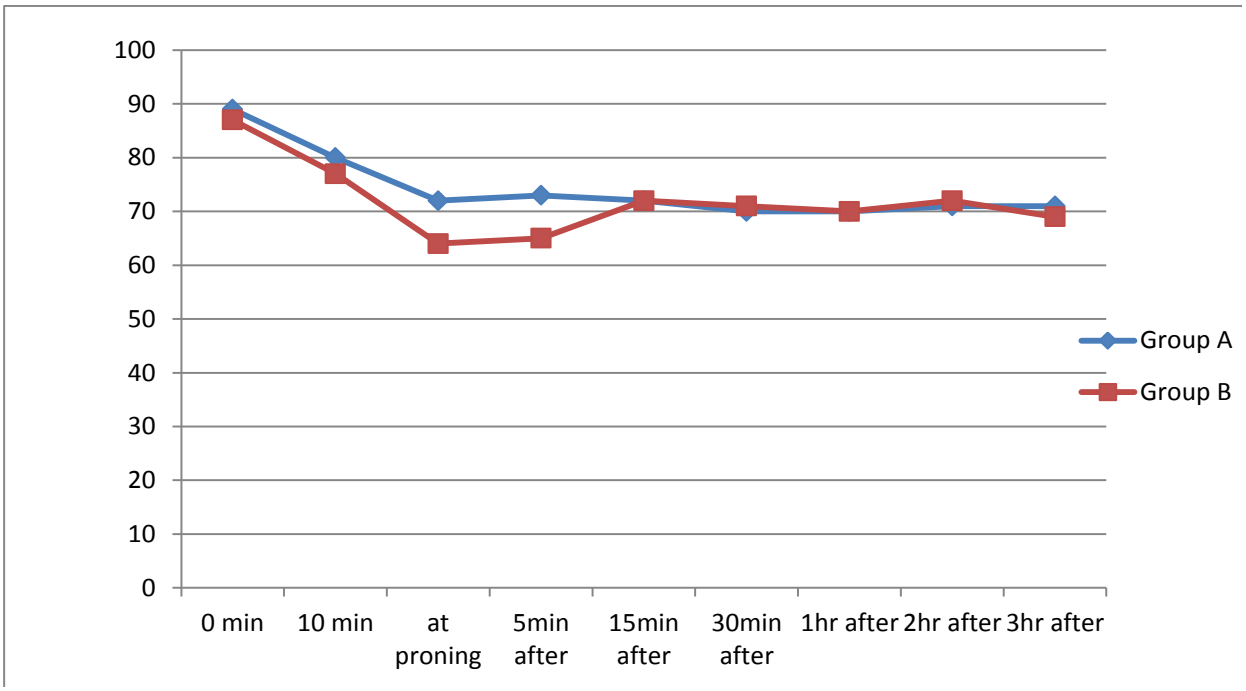
MEAN BLOOD PRESSURE (MBP)

There was no significant differencebetween both the groups inmean blood pressureat the start of bolus study drug infusion. At the end of bolus study drug there was 12% decrease in DBP in Group B (Dexmedetomidine) compared to 11%decrease in Group A (Clonidine) which was not statistically significant (Table 5). Both the groups had drop in MBP after proning compared to the supine value. Patients in Group B (Dexmedetomidine) had 27% drop in DBP at proning compared to Group A (clonidine) that had 20% drop which was statistically significant withthe P value of 0.02.

Table 5: Changes in MBP between two groups at various time points of the study.

Mean BP	Group A (clonidine)	Group B (Dexmedetomidine)	P Value
0min (start of study Drug bolus)	89.54±12.21	87.24±11.37	0.420
10 min (end of study drug bolus)	80.78±19.32	77.36±16.89	0.435
At proning	72.78±17.55	64.27±13.30	0.026
5mins after proning	73.02±14.79	65.81±11.82	0.028
15mins after proning	72.89±14.12	72.36±9.43	0.856
30mins after proning	70.13±13.13	71.63±11.49	0.614
1hr after proning	70.05±12.73	70.90±10.58	0.765
2hrs after proning	71.64±11.80	72.12±13.50	0.876
3hrs after proning	71.64±12.02	69.31±10.64	0.483

Figure 5: Changes in MBP between two groups at various time points of the study.



END TIDAL ISOFLURANE CONCENTRATION (Et Iso%):

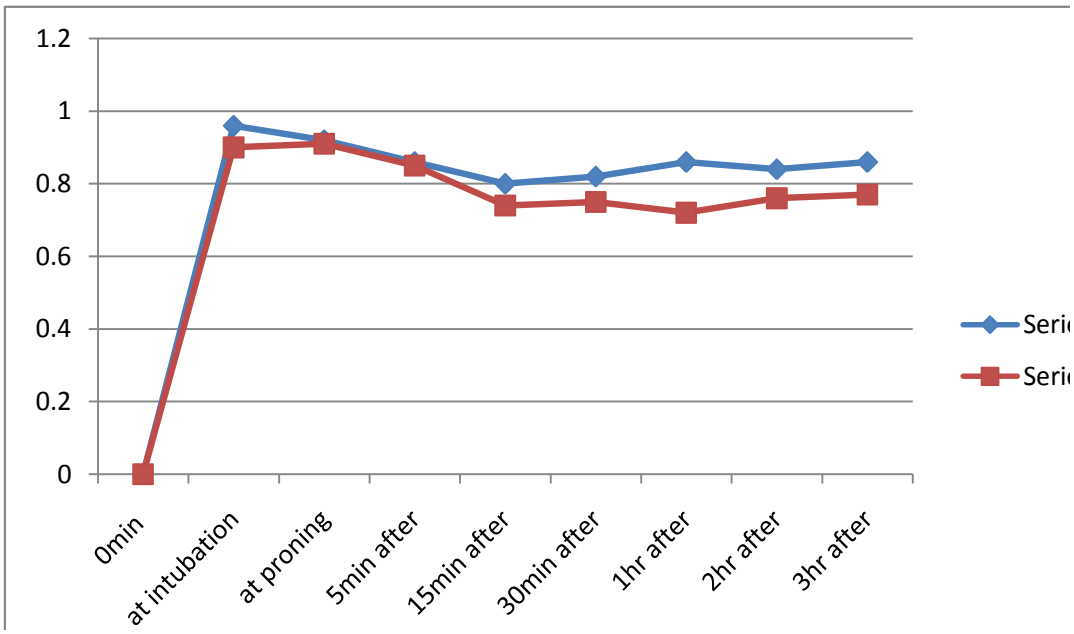
The end tidal isoflurane concentration which required to keep the BIS between 40-50 was similar between the two groups at intubation, 1,5 and 15 min after proning (Table 6).

But there was a significant difference between the two groups were noted at one hour and two hours after the prone positioning with the P value of <0.001 at one hour and P<0.039 at two hours.The end tidal isoflurane concentration in group B (Dexmedetomidine) was lower compared to the end tidal concentration of isoflurane inGroup B (clonidine group)

Table 6: End tidal concentration of isoflurane at various time interval:

Et Iso	Group A Clonidine	Group B Dexmedetomidine	P Value
At intubation	0.96±0.27	0.90±0.17	0.325
At proning	0.92±0.24	0.91±0.22	0.869
5mins after proning	0.86±0.21	0.85±0.21	0.928
15mins after proning	0.80±0.16	0.74±0.17	0.121
30mins after proning	0.82±0.17	0.75±0.14	0.060
1hr after proning	0.86±0.17	0.72±0.12	0.001
2hrs after proning	0.84±0.14	0.76±0.17	0.039
3hrs after proning	0.86±0.22	0.77±0.13	0.088

Figure 6: End tidal concentration of isoflurane at various time interval:



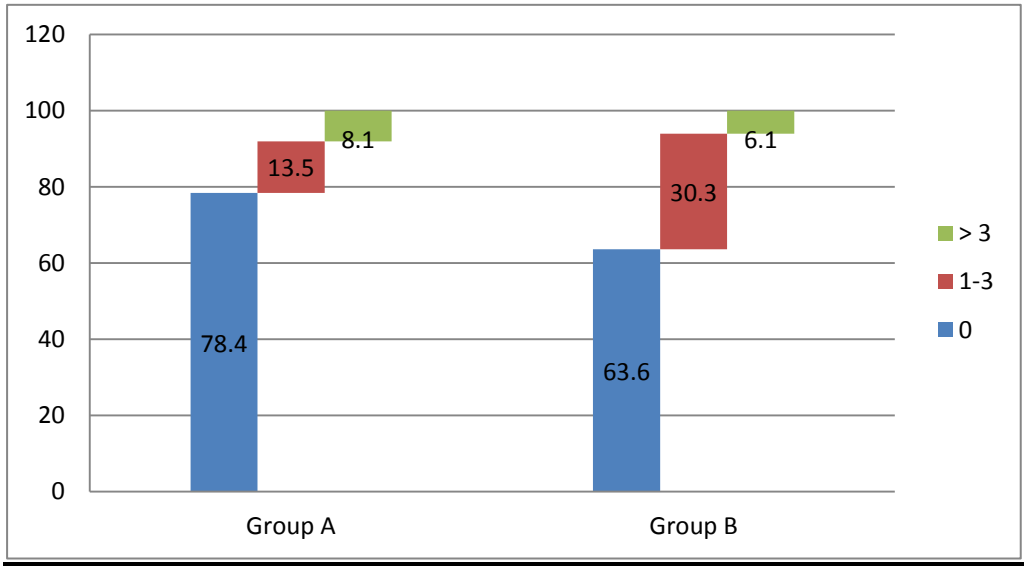
EPISODES OF HYPERTENSION

29 (78.4%) patients in Group A (clonidine) and 21 (63.6%) patients in Group B (Dexmedetomidine) did not have any hypertensive episodes (Table 7). Hypertensive responses which needed treatment was more in Group B patients who received i.v Dexmedetomidine in the perioperative period (n=12) compared to Group A patients who received clonidine premedication (n=8). All of those patients who had hypertension were treated with boluses of propofol (0.5 mg/kg) and fentanyl (0.5 ug/kg) intravenously.

Table7: Episodes of hypertension during the study period.

Episodes of Hypertension	Group A (Clonidine) No of patients (%)	Group B (Dexmedetomidine) No of patients (%)
0	29 (78.4%)	21 (63.6%)
1-3	5 (13.5%)	10 (30.3%)
>3	3 (8.1%)	2 (6.1%)

Figure : 7 Episodes of hypertension during the study period.



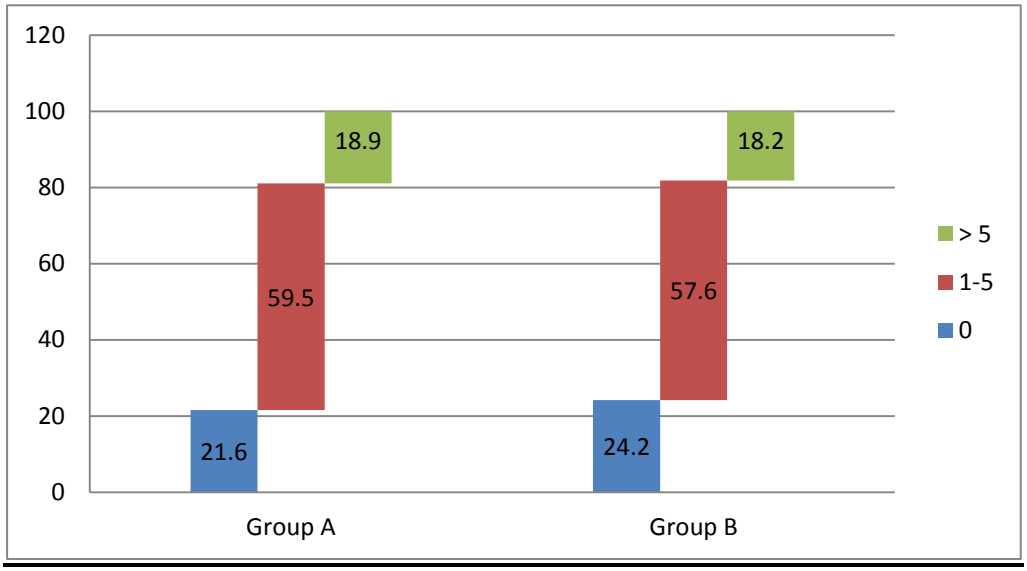
EPISODES OF HYPOTENSION

There were 8 in each group who did not have any hypotensive episodes. There were 22 patients (59.5%) in Group A (clonidine) and 19 patients (57.6%) in Group B (Dexmedetomidine) had 1-5 episodes of hypotension. 7 Patients (18.9%) in Group A(clonidine group) and 6 patients (18.2%) in Dexmedetomidine group who had more than 5 episodes of hypotension (Table 8). These hypotensive episodes were treated with small boluses of ephedrine 6mg or phenylephrine 50ugm intravenously, all patients responded well to the treatment and none of them had any refractory hypotension.

Table 8: Episodes of Hypotension during the study period.

Episodes of Hypotension	Group A (Clonidine) No of patients (%)	Group B (Dexmedetomidine) No of patients (%)
0	8 (21.6%)	8 (24.2%)
1-5	22 (59.5%)	19 (57.6%)
>5	7 (18.9%)	6 (18.2%)

Figure : 8 Episodes of Hypotension during the study period.



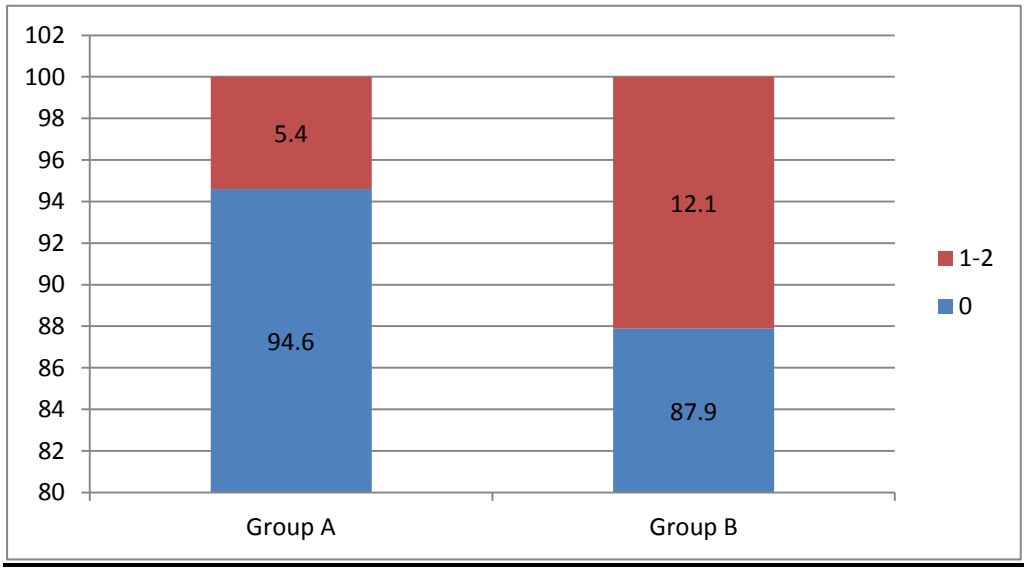
EPISODES OF BRADYCARDIA

35 (94.6%) patients in Group A (Clonidine) and 29 (87.9%) patients in Group B (Dexmedetomidine) had no episodes of bradycardia. There were 2 patients (5.4%) in Group A (clonidine) who had 1-2episodes of bradycardia, out of 2 patients; one had significant bradycardia where heart rate dropped less than 50/min,which was treated with atropine. Although there were 4 patients in Group B (Dexmedetomidine) who had one episodes of bradycardia (HR dropped < 60/min), none of them needed treatment.

Table 9: Episodes of bradycardia during the study period.

Episodes of Bradycardia	Group A (Clonidine) No of patients (%)	Group B (Dexmedetomidine) No of patients (%)
0	35 (94.6%)	29 (87.9%)
1-2	2 (5.4%)	4 (12.1%)

Figure : 9 Episodes of bradycardia during the study period.



TOTAL DOSE OF PROPOFOLAND FENTANYL REQUIRED DURING THE STUDY PERIOD.

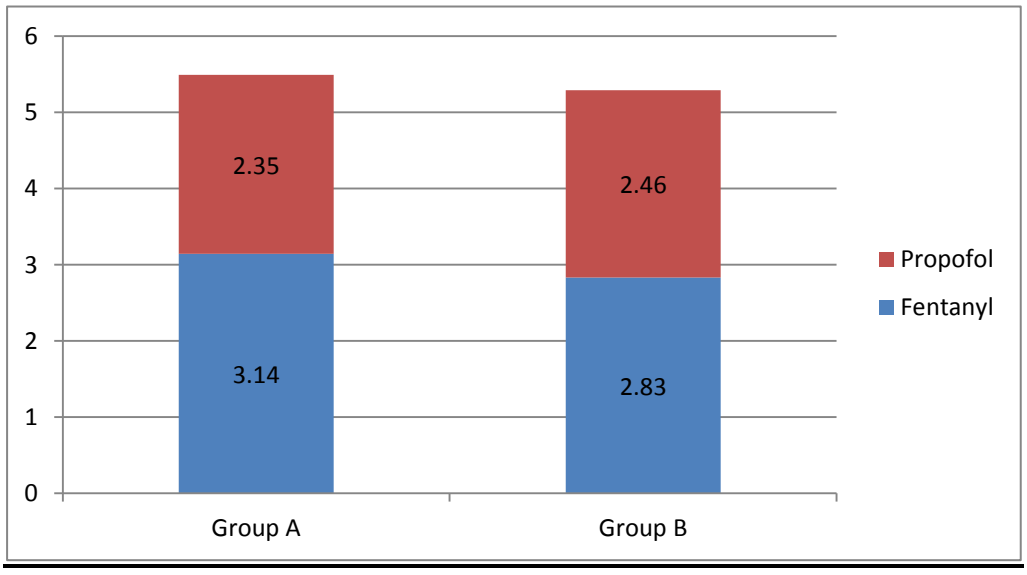
All study patients received 2 µg/kg of fentanyl at the time of induction and 0.1mg/kg of intravenous morphine after proning before surgical incision and 1gm of intravenous paracetamol for analgesia.Since adequate analgesics was given the hypertensive responses were treated initially with 0.5mg/kg of bolus dose of propofol, if blood pressure did not come to baseline value within few minutes then fentanyl (0.5µg/kg) bolus was given.

The total dose of propofol and fentanyl was given during the intraoperative period was converted as mg/kg and µg/kg respectively. There were no significant difference between two groups in the dose of propofol and fentanyl consumption(Table 10).

Table 10: Total dose of fentanyl and propofol during the study period.

Total Dose	Group A (clonidine)	Group B (Dexmedetomidine)	P value
Fentanyl (µg/kg)	3.14±0.93	2.83±1.05	0.206
Propofol (mg/kg)	2.35±0.94	2.46±1.03	0.644

Figure : 10 Dose of fentanyl and propofol used . (Mean)



TIME OF AWAKENING

The time taken between stopping of inhalational agents to the time of extubation was taken as awakening time. Awakening time was 9.81±5.15min for the Group A (Clonidine) and 8.51±3.79 min for Group B (Dexmedetomidine). But this difference was not statistically significant.

Table 11: Awakening Time

	Group A (clonidine)	**Group B (Dexmedetomidine)**	**P value**
Time of Awakening (minutes)	9.81±5.15	8.51±3.79	0.239

DURATION OF SURGERY AND THE INTRAOPERATIVE BLOOD LOSS

The average duration of surgery was comparable for both groups. The average amount of blood loss in Group A (Clonidine) was 350 ± 218 ml while in Group B (Dexmedetomidine) was 340 ± 103 ml. The blood loss was comparable between two groups.

Table 12: Duration of Surgery and Blood loss:

	Group A (clonidine)	**Group B (Dexmedetomidine)**
Duration of Surgery (hours)	3.68±1.09	3.37±0.90
Average blood loss (millilitre)	350 ± 218	340 ± 103

DISCUSSION

DISCUSSION

Recently there has been a great interest in use of perioperative systemic α 2 agonists to decrease the peri-operative opioid consumption, pain intensity, and nausea. There have been various studies on clonidine or Dexmedetomidine andits effects on anesthetic requirement, haemodynamicsand intra operative and post- operative opioid requirement comparing with placebo. There was no study comparing the effect of clonidine VsDexmedetomidine onanaesthetic requirement and haemodynamics and recovery from anesthesia.

Clonidine has been used in anesthesia practice for long time, but Dexmedetomidinehas been introduced in anaesthesia practice very recently and getting popular for its more selectivity on the alpha 2 receptor (8 times more compared to clonidine). Because of more selectivity, the complication of alpha 2 agonist induced side effects like hypotension and hypertension and bradycardia are less also it has shorter half- life (1.5 -2 hrs.) compared to clonidine (8-12 hrs.).

In our study we have compared the effects of two different drugs on the same pharmacological group given through two different routes because of the following reason:

1. Clonidine has 100% bioavailability after oral administration with an onset of action at 30- 60 mins with the peak action at 90mins and the elimination half -life of 12 (mean) hrs. Because of this pharmacological property oral preparation is as effective as intravenous drug.

2. The oral form of clonidine is cheaper and easy to administer with less side effects compared to intravenous clonidine where the drug has to be given slowly as an infusion need intravenous line and syringe pump and monitors to check the vital signs during the during the bolus infusion.

3. In our institution, it is a routine practice to give oral clonidine premedication for spine surgeries where there is no contraindication for giving this drug, to provide controlled hypotension and to reduce the haemodynamic response during the painful stimuli so we wanted to compare this routine technique with the newer alpha 2 agonist, the Dexmedetomidine. Since oral preparation of Dexmedetomidine was not available, also it has shorter duration of action we have decided to give an intravenous bolus followed by an infusion.

Both the drug effects were comparedon the anaesthetic requirement, haemodynamic effects during surgery and recovery from anaesthesia in patients undergoing two or more levels of instrumented spinal fusion.

Effect on anaesthetic requirement:

In our study we have used BIS monitor to assess the depth of Anaesthesia. End tidal Isoflurane concentration (Etiso %) was titrated to keep the BIS between "40-60". We found that the Et iso (%) concentration was similar between the two groups during intubation, at after prone position, and 15 min after prone position. At 30 min, 1 hr. and 2 hrs. after prone position, the isoflurane concentration to keep the BIS between 40-60 was significantly less in the Dexmedetomidine group compared to clonidine premedication group. This can be explained by, the peak effect of Dexmedetomidine takes 30 min after intravenous administration that is why, the Et iso concentration till 30mins after prone position was similar in both the groups after 30mins there was a significant reduction in Et iso concentration till 2 hrs. Administering the Dexmedetomidine 30 min prior to starting of surgery could have produced significant reduction in Etiso from the beginning but this was not feasible in our study.

Both the groups had reduction in Etiso from 1.15% (to produce 1 MAC) which is considered to be the standard concentration to produce 1 MAC. Since we did not have the placebo group to compare we have taken the ET iso of 1.15% as base line and calculated the difference. At intubation there was 17% (Et 0.96)reduction in Et iso concentration in clonidine group and 22% (Et iso 0.9%) reduction in Et iso concentration in

Dexmedetomidinegroup compared to the baseline value. 1 hour after prone position there was a reduction of about 26% (Et iso 0.86%) in clonidine group, and 38% (Et 0.72%) reduction in Dexmedetomidine group compared to base line. At 2 hrs. of after prone position there was 27% (0.84%) reduction in clonidine group and 34% (Etiso 0.77%) in Dexmedetomidine group.

Woodcock TE et al in their study observed that, with single dose of clonidine premedication (600 µg) reduced the isoflurane concentration from 2.3% in control group to 1.4% in clonidine group to produce controlled hypotension (40% reduction in Et iso) in patients undergoing ENT surgery.

Marchal JM et al in their study observed that, with single dose of clonidine premedication (300µg) reduced the mean isoflurane concentration from 1.01% in control group to 0.63% in clonidine group to produce controlled hypotension (37% reduction in Et iso) in patients undergoing ENT surgery.

In our study weobserved that, with single dose of clonidine premedication (200µg) reduced the Et iso % by 26, 27 % during surgery at 1 hr. 2hrs).

Khan et al studied the effect of two different concentration of Dexmedetomidine infusion on isoflurane requirement in healthy volunteers to tetanic stimulus. They have proved that the Et Iso was o.52% (50%

reduction compared to placebo) in volunteers who received 1.35ug/kg/hr., Etiso was 0.74 % ((29% reduction compared to placebo) when they have received 0.3 ug/kg/hr.

Ghodki et alstudied the effect of Dexmedetomidine on isoflurane requirement on patients undergoing laparoscopic surgeries under general anesthesia with Oxygen, Nitrous oxideand Isoflurane, where 1 µg/kg bolus followed by 0.2 µg/kg/hr. infusion of Dexmedetomidine was given during the intraoperative period. They have observed that there was a 62.5% reduction (0.75 mg/kg) in the induction dose of propofol, with a 30% less end-tidal concentration of isoflurane requirement for maintenance of anaesthesia.

Aho et al studied the effect of Dexmedetomidineinfusion onanaesthetic requirement in patients undergoing surgery under isoflurane + N2O anaesthesia and proved reduction in isoflurane concentration was more than 90%. This may be due to the combination of N2O with isoflurane.

In our study we have observed that, with 1µg/kg bolus followed by 0.5 µg/kg/hr.Dexmedetomidine there is 35-38% reduction in anaesthetic concentration during surgery (at 1hr, 2 hrs.) under isoflurane, air, oxygen anaesthesia.

Reduction in Anaesthetic concentration was comparable with other studies using clonidine and Dexmedetomidine separately comparing with placebo. We want to conclude that both the agents reduce the anaesthetic requirement but theDexmedetomidinereduces more compared to clonidine. This reduction was statistically significant.

Haemodynamic response :

Heart rate: Both clonidine premedication and Dexmedetomidine infusion are known to attenuate the heart rate response to surgical stress. In our study, throughout the study period both groups had comparable heart rate ranging from 70-80/min, which explains that both, clonidine and Dexmedetomidine attenuate the heart rate response related to surgical stress.

There was a significant difference in the baseline heart rates at the time of administration of the study drug bolus between two groups. This can be explained by, Patients in clonidine grouphad premedication (clonidine 200 µg), and so their heart rate was lower compared to patients in Dexmedetomidine group where, none of them had premedication. At the end of bolus infusion there was no difference in heart rate was noted between the two groups. During surgery both groups had comparable heart rates, there was no significant difference between two groups.

Since we did not have placebo group to compare the heart rate from baseline, the % change was not calculated for the clonidine group. Dexmedetomidine group did not receive any premedication, so the base line heart rate was compared with the heart rate after the bolus injection and the % change was calculated. There was 13% reduction in heart rate after the bolus injection (1 µg/kg). It was statistically significant.

Blood pressure:

The blood pressure changes could be attributed to various factors such as prone positioning, anaesthetic induced vasodilatation, surgical blood loss and the use of alpha 2 adreno receptor agonistic activity. Since all the parameters were comparable between the two groups except the use of two different drugswe have compared the haemodynamic effects between two groups.

In our study both clonidine and Dexmedetomidine both reduced the blood pressure. During the bolus injection of Dexmedetomidine, there was 13%, 13%, 12% reduction in the systolic, diastolic and mean blood pressure respectively. While in clonidine group there was 11%, 9%,12% reduction in systolic, diastolic and mean blood pressure respectively.

At 1 hr. after proning, during surgery when the Dexmedetomidine infusion was going on at 0.5µg/kg/hr. there was 25%, 18%, 20% reduction in systolic, diastolic and mean blood pressure respectively. While in clonidine group there was 24%, 20%, 22% reduction in systolic, diastolic and mean blood pressure.

At 2 hrs.and 3 hrs. after proning, the blood pressure reduction was comparable between two groups.

At the time of proning to 15 min after proning, the blood pressure drop was more significant in Dexmedetomidine group compared to clonidine group this may be due to the peak effect of Dexmedetomidine effect on the blood vessels.

We want to conclude that both the drugs were very effective to produce controlled hypotension during surgery, since the drop was more significant till 15 min after prone position in Dexmedetomidine group, we have keep this in our mind and treat the blood pressure promptly before it drops down significantly.

Propofol and Fentanyl requirements during the study period:

There was no significant difference between the two groups in requirement of propofol or fentanyl during the study period . The total dose of fentanyl given during the study period was 3.1 µg/kg in the clonidine group and 2.8µg/kg in theDexmedetomidine group.

The total dose of propofol given during the study period was 2.3 mg/kg in clonidine group and 2.4mg/kg in Dexmedetomidine group.

This result signifies that both clonidine and Dexmedetomidine reduce the analgesic and propofol requirement effectively.

Intraoperative blood loss:

Clonidine and Dexmedetomidine are the drugs commonly used to produce controlled hypotension by virtue of their alpha 2 agonistic action. In our study blood loss was comparable between both the groups. The mean blood loss was 350 ml in clonidine group and was 340 ml in Dexmedetomidine group.

In a double- blinded, randomized clinical trial, by **Anvari** et al evaluated the effect of oral clonidine premedication (200µg) on blood loss in lumbar spine fusion surgery under anaesthesia with propofol and remifentanil. The Mean

blood loss in the clonidine group was 422 ml compared to control group where the mean blood loss was 749 ml.

In our study we the mean blood loss was 350 ml which was comparable with Anvari et al study.

El-gohary and his associate compared the efficacy of Dexmedetomidine with sodium nitroprusside as hypotensive agent in scoliosis surgery and found that the blood loss andtransfusion requirement were significantly lower in the Dexmedetomidine group.

In a double- blinded, randomized clinical trial, by **Anvari** et al evaluated the blood loss in patients undergoing lumbar spine fusion surgery, where the mean blood loss in the control group was 749 ml, taking this as control the mean blood loss in patients who received Dexmedetomidine was 340 ml.

We want to conclude that both clonidine and Dexmedetomidine was equally effectiveto produce controlled hypotension thereby reducing the blood loss.

Awakening Time:

The awakening time was measured in minutes from the time of stopping of isoflurane to the time of extubation. The mean awakening time was 9.8 min in clonidine group and 8.5 min for Dexmedetomidine group. There was no significant difference in awakening time between the two groups.

We conclude that both, clonidine and Dexmedetomidine do not cause delay in recovery from anaesthesia.

COMPLICATION

COMPLICATION

Hypotension and bradycardia were the common complications noted after administration of alpha 2 receptor agonist. Hypertension is reported during the administration of bolus dose of Dexmedetomidine because of vaso-constrictiveeffect on the blood vessel. In our study, out of 33 patients who received Dexmedetomidine only one patient (3%) had hypertensive response during the bolus injection which was settled down on its own within 5mins.

There were 2 patients (5.4%) in clonidine and 4patients (12.1%) in Dexmedetomidine group who had bradycardiaepisodes (HR<60/min). None of these patients except one in clonidine group whose HR was dropped to 45/min needed treatment with atropine.

CONCLUSION

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Both clonidine and Dexmedetomidine reduces the endtidal concentration of Isoflurane but the Dexmedetomidine reduces more significantly compared to clonidine. Intraoperative requirement of propofol and fentanyl was same with both clonidine and Dexmedetomidine.

Both clonidine and Dexmedetomidine effectively control the heart rate in the intraoperative period. Both the drugs were very effective to provide controlled hypotension during surgery. But there is a significant drop in blood pressure at the time of proningand 5 min after proning inDexmedetomidine group compared to clonidine group. The recovery from anaesthesia was not delayed in both the groups.

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ANNEXURES

PROFORMA

Name : Age/sex :

Hospital No : Serial No :

Preinduction BP:

Study drug (Bolus) time of starting:

Infusion starting time : Stopping time :

Time of stopping the isoflurane : Time of Extubation :

Time taken for recovery: Duration of surgery :

Total Propofolused :

Haemodynamic Variables during the intra operative period.

Time	HR/ min	BP (mm of Hg) (syst/dias/mean)	End tidal Iso	MAC of Iso	BIS
0 min(baseline)					
5 min (after Bolus)					
10 min					
15 min					
20 min					
After proning (Immediately)					
5 min after					
10 min					
15 min					
30 min					
45 min					
1 hr.					
1 hr. 15 min					
1 hr. 30 min					

1 hr. 45 min					
2 hr.					
2 hr. 15 min					
2 hr. 30 min					
2hr 45 min					
3 hr.					
3 hr. 15 min					

ABREVATIONS

α 2 agonist - Alpha 2 agonist

ASA- Amrican Society of Anaesthesiologists

BIS – Bi Spectral index

CABG – Coronary Artery Bypass Graft

CNS – Central Nervous System

D&C – Dilatation And Curettage

DBP – Diastolic Blood Pressure

ECG -Electro Cardio Graph

EEG –Electro Encephalo Gram

Et Iso- End Tidal Isofluorane

ETT – Endo Tracheal Tube

FGF – Fresh Gas Flow

IRB – Institutional Review Board

IV – Intra Venous

MAP – Mean Arterial Pressure

MBP – Mean Blood Pressure

ml – millilitres

mg/kg – milligram per kilogram

mm hg – millimeters of mercury

µgm – microgram

µgm/kg – microgram per kilogram

µgm/kg/hr – microgram per kilogram per hour

mins – minutes

MAC – Minimum Alveolar Concentration

NIBP – Non Invasive Blood Pressure

NSAID - Non Steroidal Anti Inflamatory Drugs

PONV – Post Operative Nausea Vomiting

REM – Rapid Eye Movement

Sl.No – Serial Number

SBP – Systolic Blood Pressure

Vs - Versus

Department of Anaesthesia **Informed consent form no .....**

CMC hospital Vellore, Tamilnadu

Patient information sheet

1. The title of my research is "A randomized control trial to compare the effect of Dexmedetomidine infusion in the perioperative period Vs oral clonidine as premedication, on anaesthetic requirements, haemodynamics and recovery from anaesthesia in patients undergoing major spine surgery."

Person carrying out research: Dr.Hari Narayana Prabhu

I'm Dr.Hari Narayana Prabhu, a senior registrar working in the department of Anaesthesia, CMC Vellore. I'm doing a research study to compare the effect of Dexmedetomidine on heart rate, blood pressure changes, anesthetic requirement and recovery from anaesthesia with Tab. Clonidine as premedication in patients undergoing major spine surgery

I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask me or the anaesthesiologist on the day of surgery.

Purpose of the research:

Spine surgery is associated with lot of bleeding, fluctuations in blood pressure and heart rate during the surgery. Usually these surgeries will take approximately about 4 hours. There are techniques used to reduce the bleeding, swings in the blood pressure and heart rate and faster recovery from anaesthesia. One of these techniques is using a particular group of drug (Alpha 2-adrenoceptor agonist) to provide drop in blood pressure in a controlled manner. This technique helps the surgeon to performthe operation faster because of the bloodless field which in turn reduces the blood loss and operative time, also helps the patients to recover fast from anaesthesia.

One of the drugs in this group is clonidine and it has been in use during or before surgery for a considerable period of time for reducing the blood pressure in a controlled manner. It also produces sedation and pain relief. Dexmedetomidine is a new drug, which produces good pain relief and sedation and compared to clonidine because it acts on the specific site and is thought to produce less side effects. Both these drugs are being used in anesthetic practice. In this study we are comparing the two to see if Dexmedetomidine is superior to Clonidine in reducing the amount of anaesthesia drug needed to keep you in a sleep state during surgery, blood pressure and heart rate changes and the time to waking up from anaesthesia.

You are being requested to participate in thisstudy, if you give your consent the above mentioned medications will be given to you based on random allocation. You will receive either of the drugs.

I plan to include patients who undergo surgery on the spine or back bone. Your participation in this study is purely voluntary and you can withdraw from the study at any time, even immediately before the surgery. Your refusal to participate will not involve any penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate in this research project, you will receive the routine treatment for this operation.

Confidentiality: your name will not be mentioned anywhere neither the data sheet nor the final published study. Your data will bear a study number and the number will be used till analysis. The master sheet will have your study number.

Reimbursements: You will not be charged the cost of Dexmedetomidine. There are no other incentives.

Sharing of the result: The results of research are property of Christian medical college and I'm entitled to publish it in a journal or present in a conference.

This proposal has been reviewed and approved by [IRB, ChristianMedicalCollege], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB,

Contact
Research Office,
Second floor,Carman block,
ChristianMedicalCollege,
Bagayam, Vellore 632002.
Email: research@cmcvellore.ac.in, Telephone: 04162284294.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

In case of doubts or questions, please contact Dr.Hari Narayana Prabhu, Department of Anaesthesia, ChristianMedicalCollege and Hospital, Vellore. Ph.No. 9894726616.

PART II: Certificate of Consent

I have read the foregoing information/ it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate Thumb impression (R / L)

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ and **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Inj. Dexmedetomidine or Placebo will be given during surgery.
2. Participation is voluntary and cost of Dexmedetomidine will be borne by the research fund.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

SNO	age	sex	IP_no	GROUP	wt_of_pt_kg	Heart_rate0 min	Heart_rate_B OLUS_10min	Heart_ rate_at_proni ng	Heart_ rate5min	Heart_ rate15min	Heart_ rate30min	Heart_ rate1hr	Heart_ rate2hr	Heart_ rate3hr	Heart_ rate4hr

Print Name of Researcher/person taking the consent-Dr. Hari Narayana Prabhu

Signature of Researcher /person taking the consent_____

Date _____

1	49	f	104628f	A	52	72	83	68	60	76	60	62	77	78	
2	67	m	160880f	B	63	70	66	71	68	77	79	80	83		
3	64	f	053843f	A	65	71	72	82	84	73	66	99	100		
4	22	m	127066f	B	62	67	70	60	58	64	62	56	58	59	
5	54	f	713103a	A	59	96	86	87	84	80	81	79	76	74	
6	42	m	157074f	A	49	77	74	78	76	67	62	64	72	75	
7	70	m	717610c	A	52	105	85	96	93	85	93	92	88	93	
8	67	f	965929d	B	58	106	93	92	86	78	76	72	101		
9	47	f	680932d	B	50	115	89	84	74	63	65	60	74	78	
10	30	f	121732f	B	60	87	73	71	66	65	64	63	71	90	
11	51	m	653116b	B	58	113	82	110	102	89	93	88	88	96	
12	39	m	879161b	B	64	100	80	78	79	76	77	81	77	83	85
13	58	f	172604f	A	65	79	69	68	69	74	70	71	81	85	86
14	38	m	844513c	A	68	110	109	108	101	97	95	93	90	88	96
15	48	f	192654f	B	45	88	69	84	93	92	77	81	74		
16	48	m	182444f	A	52	67	71	163	117	76	59	75	73		
17	35	f	210134f	B	63	137	137	76	63	125	148	56	68	72	
18	41	f	220853f	A	61	116	95	103	93	93	86	84	82	85	91
19	35	f	167725f	B	57	106	82	67	68	69	66	69	71		
20	61	m	188599f	A	59	79	82	54	61	55	54	59	61	63	61
21	51	f	226019f	B	54	95	80	75	76	71	68	69	71	70	73
22	67	m	223565f	A	58	74	69	82	90	87	72	73	72	78	70
23	55	f	420646d	B	52	91	91	96	94	94	96	86	86	90	100
24	55	f	086919f	A	70	85	80	84	65	64	68	68	76		
25	42	m	224638f	A	60	70	68	88	96	87	92	88	96		
26				B											
27	31	f	232624f	A	57	75	106	92	88	82	82	69	85	93	106
28	55	m	031686f	B	50	65	57	63	61	51	56	62	73	83	84
29	56	m	232947f	A	56	71	66	70	62	63	66	62	67	71	
30	55	f	549851c	B	62	70	61	75	66	65	62	64	64	67	
31	72	m	827619c	B	49	64	66	65	61	56	55	57	56	61	65
32	46	f	237765f	A	50	73	73	71	71	63	64	75	74	77	
33	23	m	221451f	B	54	72	70	61	63	60	65	90	63	72	70
34	18	m	240733f	A	60	76	74	89	99	80	76	80	87	94	96
35	27	f	226165f	A	56	67	70	60	58	64	62	56	58	59	
36	29	m	231639f	B	70	82	78	69	72	66	66	64	87		
37	43	m	239359f	A	62	76	70	84	82	76	68	75	72		
38				B											
39	56	m	201771f	B	49	72	69	66	76	77	76	68	72	72	
40	63	f	201598f	A	51	85	79	69	70	66	80	64	64	70	75
41	37	f	230208f	A	60	68	78	62	70	61	98	65	62	78	
42	50	m	254932f	B	53	100	95	106	99	82	84	85	92		
43	46	m	235105f	B	50	100	87	76	70	61	62	66	63	68	
44	54	f	242501f	A	61	68	55	50	49	51	52	57	58	65	
45	40	m	172876f	A	75	75	68	75	73	77	87	85	93	76	78

46	44	f	021234f	B	64	65	60	65	61	59	57	70	71		
47	49	m	225571f	A	69	78	66	67	67	65	65	63	67		
48	31	f	237531f	B	56	93	94	83	81	70	62	61	68	69	
49	60	m	752029d	A	66	82	84	96	91	92	89	93	97	93	
50	47	f	256759f	B	62	67	68	54	53	56	54	58	62	68	
51	28	m	261541f	B	63	130	99	115	105	87	95	88	99	89	81
52	52	f	254209f	A	53	79	81	105	99	72	66	69	74	86	83
53	42	f	025185f	A	59	76	70	67	68	61	56	60	70	70	
54	21	f	253949f	B	50	108	90	87	78	71	65	64	65	71	74
55	39	m	269370f	A	60	50	49	74	74	77	70	68	73	77	
56	39	f	251257f	A	61	72	77	94	95	72	66	81	61	70	
57	39	m	277192f	B	75	103	77	80	80	79	71	67	74	75	
58	57	m	216662f	B	63	113	82	110	102	89	93	88	88	96	
59	45	f	179150f	A	61	94	85	88	89	74	74	65	68		
60	59	m	137430f	B	70	74	68	70	68	62	61	65	66	66	
61	44	f	265754f	A	59	75	79	70	77	70	71	62	66	67	
62	45	f	255939f	B	70	70	68	60	100	90	80	88	91		
63	34	m	085900d	B	74	66	68	100	106	70	73	70	87	98	95
64	62	m	281585f	B	52	82	78	69	72	66	66	64	87		
65	72	m	297409f	A	50	85	77	81	81	81	82	101	96	101	
66	62	f	647712o	A	69	80	75	71	79	66	67	73	88		
67	49	f	219570f	A	65	90	90	110	99	94	95	107	97	91	
68	42	m	269108d	A	77	80	77	74	74	73	78	74	69	75	
69	33	m	198291f	B	72	82	69	72	67	91	86	82			
70	40	f	287983f	B	66	91	73	70	69	67	68	88	80	82	
71	67	f	192733f	A	58	116	109	93	86	85	84	84	85	85	87
72	42	m	231762d	A	63	103	99	84	68	76	78	67	86	87	

SNO	Heart_ rate5hr	SBP_0min	SBP_BOLUS_ 10min	SBP_at_proni ng	SBP_5min	SBP_15min	SBP_30min	SBP_1hr	SBP_2hr	SBP_3hr	SBP_4hr	SBP_5hr	DBP_0min	DBP_BOLUS_ 10min	DBP_at_proni ng	DBP_5min	DBP_15min
1		118	111	80	84	84	88	85	98	92			68	72	62	64	51
2		104	71	76	76	101	90	100	109				50	41	42	40	57
3		140	132	124	124	138	132	126	136				72	73	64	65	61
4		116	111	63	89	94	104	84	86	84			80	87	35	45	57
5		124	138	85	84	93	80	85	74	122			71	75	53	55	63
6		113	130	92	92	97	94	93	94	91			68	90	59	61	64
7		124	95	126	126	89	107	108	110	111			75	51	74	74	52
8		139	140	126	122	115	105	103	160				76	71	86	70	67
9		156	121	91	87	124	84	101	101	100			88	78	56	52	74
10		114	86	79	87	91	76	98	94	91			64	47	47	47	54
11		122	85	85	85	87	103	78	86	97			64	36	38	41	53
12	90	140	128	100	100	98	100	97	118	103	113	108	89	79	60	61	61
13		112	68	96	76	83	84	80	113	114	115		66	45	53	76	45

14		144	140	106	109	93	80	78	90	94	96		78	78	61	73	60
15		125	200	100	94	107	95	92	113				88	100	74	72	82
16		107	95	137	106	78	90	79	71				57	58	88	75	56
17		93	68	84	75	73	89	64	66	82			54	34	69	46	45
18	94	150	92	136	117	118	113	129	103	101	105	116	84	67	95	75	76
19		115	101	107	98	120	124	120	113				65	79	52	50	67
20	64	136	136	98	92	88	88	74	92	100	94	103	71	72	52	48	53
21		120	98	85	83	89	85	89	85	84	86		67	54	48	41	50
22	60	108	107	112	150	156	90	126	88	113	101	85	75	66	43	70	72
23		108	90	120	116	121	124	103	90	140	103		46	45	60	64	67
24		123	136	75	68	77	70	82	74				64	83	58	52	57
25		114	102	110	92	123	111	103	104				60	59	77	47	81
26																	
27		95	89	87	85	79	77	93	94	84	95		52	57	50	50	45
28		121	108	85	78	122	100	85	83	100	104		84	54	46	44	62
29		123	67	81	107	119	117	95	128	128			57	36	34	51	56
30		141	114	98	77	95	91	87	88	94			74	59	64	46	61
31		146	118	81	77	73	74	95	87	75	81		61	53	52	51	48
32		140	89	87	99	119	118	78	97	97			90	52	57	65	72
33	68	107	104	80	81	90	100	85	93	87	94	103	58	54	48	39	40
34	91	98	94	104	115	90	85	79	79	84	82	89	57	51	61	75	53
35		116	111	63	72	94	104	84	86	84			80	87	32	35	57
36		137	124	89	91	100	91	90	119				72	68	49	53	62
37		146	143	154	129	120	88	113	92				80	82	82	84	78
38																	
39		140	116	72	90	93	103	102	90	90			90	74	40	46	47
40	77	140	140	86	85	118	156	118	110	136	116	121	67	64	49	50	60
41		134	106	90	87	89	100	93	100	89			70	60	55	56	53
42		115	113	100	105	100	110	106	128				74	69	67	71	58
43		130	114	70	108	103	98	122	87	108			70	65	50	69	67
44		160	180	80	79	89	97	105	100	165			82	68	40	39	47
45		96	94	99	100	130	120	106	130	95	90		60	63	60	58	78
46		109	139	88	93	104	123	112	121				66	75	51	47	51
47		128	105	80	103	109	90	77	89				78	55	68	75	68
48		125	120	104	95	91	93	86	90	94			60	60	50	53	50
49		125	120	76	91	134	103	94	104	97			58	57	44	45	57
50		119	73	98	87	93	80	82	88	108			73	57	49	46	47
51		106	87	84	61	87	125	89	111	78	83		88	60	63	45	60
52	83	113	120	150	150	120	114	110	105	80	85	84	62	68	90	90	70
53		121	110	99	108	88	80	83	88	103			65	61	55	66	50
54		137	119	90	87	91	90	96	100	90	96		81	73	51	52	58
55		150	126	115	108	110	120	99	124	119			72	61	54	50	55
56		128	80	106	149	99	73	111	96	102			73	40	57	50	46
57		140	111	101	109	86	107	113	82	74			80	66	67	73	75
58		122	85	85	85	87	103	77	86	97			64	36	36	41	53

59		144	138	99	105	81	80	76	100				78	68	62	59	52
60		132	85	85	110	123	90	77	88	100			70	64	64	82	83
61		135	146	97	96	120	130	105	106	84			67	75	60	55	66
62		111	105	60	91	89	95	93	97				64	73	40	61	63
63	94	127	127	96	105	92	86	123	115	104	100	91	63	62	64	55	58
64		137	124	89	91	100	91	90	114				72	68	49	53	62
65		141	116	147	130	131	127	153	106	98			59	48	58	56	52
66		151	87	70	100	81	91	98	131				87	54	40	51	42
67		149	146	122	114	120	106	144	108	131			73	72	100	58	72
68		129	84	115	96	99	96	99	103	101			65	44	54	56	55
69		123	107	97	84	109	106	109					95	59	56	44	60
70		119	108	86	89	87	82	98	89	87			69	62	49	50	48
71		150	173	111	74	88	83	90	80	92	83		75	127	46	47	50
72		130	132	104	98	88	89	96	57	77			84	65	66	45	58

SNO	DBP_30min	DBP_1hr	DBP_2hr	DBP_3hr	DBP_4hr	DBP_5hr	BP_0min	BP_BOLUS_10min	BP_at_proning	BP_5min	BP_15min	BP_30min	BP_1hr	BP_2hr	BP_3hr	BP_4hr	BP_5hr	ETISO_0min
1	52	49	59	56			82	87	58	59	62	64	60	71	68			0
2	53	58	56				66	49	51	51	68	63	69	62				0
3	60	92	92				95	92	82	81	90	84	108	110				0
4	65	51	48	45			89	91	47	53	74	82	65	62	60			0
5	52	59	47	76			84	83	61	62	70	59	65	53	85			0
6	60	62	57	53			86	92	71	73	76	72	68	71	68			0
7	60	60	61	62			86	66	94	94	64	76	76	77	80			0
8	64	64	82				90	98	112	93	86	79	78	114				0
9	42	58	60	73			103	97	69	65	94	57						0
10	43	53	50	54			75	58	56	59	66	51	67	69	68			0
11	64	46	52	58			87	53	53	60	66	80	57	66	72			0
12	63	74	71	60	64	61	113	94	72	74	74	76	83	88	74	81	77	0
13	46	44	63	64	69		77	51	67	52	58	59	56	80	81	80		0
14	52	52	60	59	61		110	109	83	85	72	60	58	70	71	80		0
15	69	75	83				97	129	81	77	88	75	79	90				0
16	55	51	45				70	66	107	86	37	67	60	54				0
17	59	41	48	49			70	48	60	55	54	70	49	55	60			0
18	62	71	68	62	62	67	110	78	111	92	92	78	89	82	77	78	84	0
19	69	66	55				76	79	69	65	82	84	81	72				0
20	51	53	53	62	53	56	86	88	67	63	65	63	66	65	75	67	72	0
21	47	63	61	58	59		90	73	63	56	65	61	63	61	58	59		0
22	43	59	79	57	50	43	93	81	66	97	101	57	82	83	75	66	56	0
23	70	61	50	90	67		61	60	82	80	83	89	74	59	100	80		0
24	55	54	64				81	103	58	52	57	55	63	70				0
25	54	58	63				80	76	64	63	82	72	72	76				0
26																		

27	44	49	49	49	52		68	71	63	62	57	55	63	63	61	65		0
28	49	44	46	64	66		92	71	46	44	82	65	56	57	75	78		0
29	56	44	61	62			79	46	51	69	76	59	84	84				0
30	61	57	59	61			101	67	59	56	73	72	68	71	72			0
31	49	55	47	45	45		82	76	61	60	57	58	68	59	55	57		0
32	72	50	62	60			116	69	69	77	89	88	60	75	73			0
33	60	52	49	41	43	39	73	73	47	55	62	64	64	63	56	58	60	0
34	52	50	50	49	51	51	71	65	77	89	66	64	61	59	60	61	62	0
35	65	51	48	45			89	51	44	47	74	82	65	62	60			0
36	61	56	64				95	87	61	66	75	65	66	80				0
37	52	80	64				105	105	109	102	94	66	91	74				0
38																		
39	59	59	54	64			100	84	49	64	59	72	72	70	68			0
40	80	66	59	70	80	61	97	92	61	61	79	107	83	75	93	95	81	0
41	66	60	67	56			86	81	68	70	67	80	72	82	70			0
42	68	58	69				83	80	74	78	73	80	76	93				0
43	64	75	52	61			94	85	63	86	82	77	96	65	81			0
44	54	55	53	89			108	110	51	50	60	67	70	66	113			0
45	68	58	70	51	45		69	71	70	73	99	90	76	92	67	62		0
46	64	61	73				85	98	62	62	69	86	78	87				0
47	57	46	54				96	74	73	86	82	68	56	66				0
48	53	45	47	49			76	82	70	70	67	70	61	73	66			0
49	47	44	49	49			80	78	52	58	79	62	57	64	63			0
50	37	41	51	55			78	61	66	62	63	53	55	60	78			0
51	92	62	84	57	55		91	67	71	50	70	106	73	95	65	65		0
52	66	72	60	42	45	43	84	87	100	100	90	86	70	76	54	58	57	0
53	41	40	39	49			89	83	73	83	64	54	54	55	67			0
54	55	61	64	57	50		94	84	64	63	68	65	73	75	66	65		0
55	53	44	58	56			92	81	69	64	68	67	55	72	71			0
56	39	58	50	53			86	55	77	88	62	50	76	66	70			0
57	66	69	51	47			94	83	80	88	81	81	87	63	57			0
58	64	47	52	58			87	53	53	60	66	80	58	66	72			0
59	52	49	50				95	85	77	76	63	62	60	60				0
60	63	57	49	55			93	64	64	82	83	63	75	62	72			0
61	77	64	65	44			108	102	74	71	86	100	79	81	56			0
62	63	60	61				84	85	45	75	77	77	73	75				0
63	56	75	63	73	59	57	83	82	74	76	70	66	92	78	85	73	70	0
64	61	56	64				95	87	61	66	75	65	66	80				0
65	50	57	47	45			79	64	87	82	76	72	85	65	62			0
66	45	49	65				103	62	52	69	55	60	66	87				0
67	56	67	59	62			99	97	112	78	89	73	93	75	85			0
68	66	59	62	58			88	57	69	72	68	82	73	77	72			0
69	59	61					101	74	71	56	74	72	74					0
70	48	59	63	54			81	81	65	65	62	60	73	66	65			0
71	47	53	48	51	47		90	139	69	58	64	60	66	58	65	59		0

72	65	44	55	54			96	92	57	58	64	75	54	55	64			0

SNO	ETISO_BOLUS_10min	ETISO_at_proning	ETISO_5min	ETISO_15min	ETISO_30min	ETISO_1hr	ETISO_2hr	ETISO_3hr	ETISO_4hr	ETISO_5hr	MACISO_0min	MACISO_BOLUS_10min	MACISO_at_proning	MACISO_5min	MACISO_15min
1	0.9	0.8	0.8	0.8	0.7	0.7	0.8	0.7			0	0.8	0.7	0.7	0.7
2	0.9	0.75	0.7	0.75	0.7	0.75	0.7				0	0.8	0.6	0.6	0.6
3	1.2	0.9	0.9	0.7	1.2	1	0.9				0	1	0.7	0.8	0.6
4	1	1.2	1	0.7	0.75	0.75	0.75	0.8			0	1	1	0.9	0.6
5	1	1.3	0.85	0.85	0.85	0.95	0.85	0.8			0		0.7	0.7	0.7
6	0.9	1.1	1.05	0.85	0.95	0.9	0.9	1			0	0.6	1.1	0.9	0.8
7	1.6	0.7	0.85	0.95	0.85	0.75	0.75	0.7			0	1.4	0.7	0.7	0.8
8	1.1	0.6	0.5	0.5	0.5	0.7	0.8				0	1.1	0.5	0.5	0.4
9	1	0.55	0.55	0.6	0.9	0.65	0.9	0.75			0	1	0.4	0.4	0.5
10	0.9	0.8	0.8	0.85	0.8	0.65	0.7	0.65			0	0.8	0.7	0.7	0.7
11	1.1	1.3	1.2	0.8	0.75	0.9	0.9	0.95			0	1	1.1	1	0.7
12	0.8	0.85	0.8	0.8	0.85	0.65	0.6	0.7	0.7	0.85	0	0.7	0.7	0.7	0.7
13	0.6	0.65	0.6	0.7	0.8	0.7	0.65	0.65	0.7		0	0.5	0.5	0.6	0.7
14	0.9	0.7	0.8	1	1.1	1	0.9	1	1		0	0.8	0.6	0.7	0.9
15	1	0.8	0.6	0.6	0.6	0.6	0.7				0	0.9	0.7	0.5	0.5
16	1.05	1	0.8	0.85	0.75	0.7	0.95				0	0.9	0.9	0.7	0.7
17	0.8	0.95	0.45	0.35	0.6	0.45	0.55	0.7			0	0.7	0.8	0.3	0.3
18	1.3	1.2	1.15	1.05	0.9	0.85	1.05	1.05	1	0.9	0	0.8	1	1	0.9
19	1.05	0.75	0.65	0.65	0.65	0.7	0.65				0	0.9	0.6	0.6	0.6
20	1.9	1	1.05	0.85	0.85	0.75	0.95	1.05	0.9	0.95	0	1.5	0.9	0.9	0.8
21	0.9	0.65	0.7	0.6	0.6	0.65	0.9	1	1		0	0.8	0.5	0.6	0.5
22	1	0.3	0.2	0.4	0.5	0.55	0.7	0.6	0.6	0.6	0	0.9	0.2	0.2	0.3
23	0.75	0.7	0.75	0.75	0.8	0.65	0.6	0.7	0.75		0	0.6	0.6	0.6	0.6
24	0.9	0.95	0.95	0.95	0.6	0.75	0.7				0	0.8	0.8	0.8	0.6
25	0.8	1	0.9	1	1	1.2	0.7				0	0.6	0.6	0.6	0.8
26															
27	1.1	1.15	1.2	1.2	1.2	0.9	0.9	1	0.95		0	1	1	1	1.1
28	0.95	0.95	0.95	0.9	0.9	0.8	1	1.1	1.2		0	0.8	0.9	0.8	0.8
29	1.3	1.4	0.7	0.6	0.5	0.8	0.6	0.8			0	1.2	1.2	0.8	0.8
30	0.9	0.5	0.4	0.45	0.55	0.55	0.6	0.6			0	0.8	0.4	0.3	0.3
31	1	0.9	0.8	0.75	0.75	0.7	0.75	0.85	0.85		0	0.9	0.8	0.7	0.6
32	0.85	0.75	0.75	0.7	0.7	0.75	0.7	0.7			0	0.7	0.6	0.6	0.6
33	0.5	0.75	0.85	0.9	0.9	0.8	0.75	0.9	0.8	0.6	0	0.4	0.6	0.7	0.8
34	0.5	0.6	0.6	0.7	0.7	1	1	0.9	1	1	0	0.4	0.5	0.5	0.6
35	1.2	1.1	1	0.7	0.75	0.75	0.75	0.8			0	1	1	0.9	0.6
36	1.1	0.95	1	1	1	0.9	1.1				0	1	0.8	0.9	1
37	0.8	0.9	0.6	0.65	0.75	0.85	0.65				0	0.7	0.8	0.6	0.6

38															
39	1	0.9	1	0.8	0.9	0.6	0.6	0.7			0	0.9	0.8	0.7	0.7
40	0.95	0.8	0.85	0.85	0.65	0.8	0.8	0.65	0.8	0.9	0	0.8	0.7	0.7	0.7
41	1	0.9	0.9	0.7	0.8	0.8	0.8	0.8			0	0.9	0.8	0.8	0.6
42	1.1	1	0.9	0.7	0.7	0.9	0.8				0	1	0.9	0.8	0.6
43	0.9	1.1	1.1	1.1	0.95	0.8	0.8	0.75			0	0.8	1	1	1
44	0.5	0.75	0.95	0.8	0.9	0.9	1.05	0.3			0	0.4	0.6	0.8	0.7
45	1	0.85	1	1	1.2	1.15	1	1.2	0.9		0	0.9	0.7	0.9	0.9
46	0.8	0.75	0.85	0.35	0.35	0.65	0.3				0	0.7	0.6	0.7	0.2
47	0.7	0.8	0.8	0.95	0.9	0.8	0.8				0	0.8	0.8	0.9	0.9
48	0.5	1.15	1.05	0.85	0.8	0.8	0.75	0.65			0	0.4	0.9	0.9	0.7
49	1	1	0.6	0.5	0.75	0.7	0.95	1.1			0	0.9	0.9	0.5	0.4
50	1.2	1.1	1	0.7	0.85	0.7	0.6	0.7			0	1.1	0.9	0.8	0.7
51	1	1.2	1.3	1	0.8	0.9	1.05	0.7	0.75		0	0.9	1	1.1	0.9
52	0.7	1.2	1.2	0.8	0.7	1	0.9	1	1	1.5	0	0.6	1	1	0.7
53	0.7	0.65	0.6	0.65	0.75	0.7	0.75	0.8			0	0.6	0.5	0.5	0.5
54	1.05	0.9	0.95	0.9	0.8	0.95	0.9	0.8	0.75		0	0.9	0.8	0.8	0.8
55	1	0.9	0.85	0.75	0.9	1.05	1.2	1.3			0	0.9	0.8	0.7	0.6
56	0.9	0.7	0.6	0.8	0.95	0.95	0.9	1.1			0	0.8	0.6	0.5	0.7
57	0.9	0.9	0.9	0.7	0.65	0.7	0.75	0.7			0	0.8	0.8	0.8	0.6
58	0.6	1.3	1.2	0.8	0.75	0.9	0.9	0.95			0	0.5	1.1	1	0.7
59	0.8	0.7	0.75	0.75	0.75	0.9	0.7				0	0.7	0.6	0.6	0.6
60	1	1.3	1.1	0.75	0.6	0.65	0.7	0.65			0	0.9	1.1	0.9	0.6
61	1	1.1	1	0.85	0.7	0.8	0.85	0.85			0	0.9	0.9	0.9	0.7
62	0.9	0.8	0.75	0.75	0.75	0.75	0.75				0	0.8	0.7	0.6	0.6
63	1	1.1	0.9	0.7	0.8	0.8	0.8	0.8	0.9	1	0	0.9	0.9	0.8	0.6
64	0.7	0.95	1	1	1	0.9	1.1				0	0.6	0.8	0.9	0.9
65	1	1.4	1.35	1	1.05	1.35	1.2	1.15			0	0.9	1.2	1.1	0.9
66	1.1	1.2	1.15	1	1	1.15	0.8				0	0.9	1	1	0.9
67	0.5	0.7	0.9	0.75	0.7	1.1	0.8	1			0	0.4	0.6	0.8	0.6
68	1.05	0.95	0.9	0.7	0.65	0.8	0.75	0.7			0	0.9	0.8	0.8	0.6
69	1	1.15	0.9	0.8	0.75	0.6					0	0.9	0.9	0.8	0.7
70	0.6	0.65	0.65	0.7	0.7	0.6	0.65	0.65			0	0.5	0.5	0.5	0.6
71	1	1.2	0.9	0.8	0.8	0.75	0.8	0.7	0.85		0	0.9	1	0.8	0.7
72	1	0.9	0.8	0.7	0.7	0.6	0.7	0.6			0	0.9	0.8	0.7	0.6

SNO	MACISO_30 min	MACISO_1hr	MACISO_2hr	MACISO_3hr	MACISO_4hr	MACISO_5hr	BIS_0min	BIS_BOLUS_10min	BIS_at_proning	BIS_5min	BIS_15min	BIS_30min	BIS_1hr	BIS_2hr	BIS_3hr	BIS_4hr
1	0.6	0.6	0.7	0.6			100	55	56	56	61	55	48	52	44	
2	0.6	0.6	0.6				100	34	42	42	45	56	48			
3	1.1	0.9	0.8				99	76	34	38	48	42	38	44		

4	0.6	0.6	0.6	0.7			95	86	39	44	54	51	54	45	49	
5	0.7	0.8	0.7	0.7			87	43	32	32	48	47	44	47	53	
6	0.8	0.8	0.9	1			97	62	33	31	47	56	56	46	42	
7	0.7	0.6	0.6	0.6			97	88	38	39	44	48	42	44	52	
8	0.4	0.6	0.7				98	82	50	48	49	34	38	42		
9	0.8	0.5	0.8	0.6			96	82	44	40	36	52	42	58	49	
10	0.6	0.5	0.6	0.5			99	82	34	38	48	52	52	48	46	
11	0.7	0.8	0.8	0.8			99	80	39	31	51	57	49	52	53	
12	0.8	0.5	0.5	0.5	0.6	0.7	94	70	44	42	46	46	48	49	48	44
13	0.7	0.6	0.5	0.5	0.6		93	26	44	45	42	45	40	42	40	62
14	1	0.9	0.8	0.9	0.9		98	98	53	55	36	41	33	39	35	33
15	0.5	0.5	0.6				84	73	32	32	44	40	35	54		
16	0.6	0.6	0.8				84	76	56	48	52	44	55	47		
17	0.5	0.3	0.4	0.6			74	30	37	37	65	42	37	44	52	
18	0.8	0.7	0.9	0.9	0.9	0.8	95	45	32	36	38	41	41	38	48	43
19	0.6	0.6	0.6				96	96	47	48	39	41	43	50		
20	0.7	0.7	0.85	0.9	0.8	0.8	97	88	49	41	41	42	41	42	39	46
21	0.5	0.6	0.8	0.9	0.9		94	84	61	60	59	44	56	53	54	30
22	0.4	0.5	0.6	0.5	0.5	0.5	97	77	43	45	48	44	46	42	40	41
23	0.7	0.6	0.5	0.6	0.7		97	50	34	32	41	40	39	40	41	40
24	0.6	0.6	0.6				97	92	43	39	32	41	54	59		
25	0.8	0.8	0.7				90	70	58	57	58	49	44	46		
26																
27	1.1	0.8	0.8	0.9	0.8		97	42	34	30	25	24	40	40	33	43
28	0.8	0.7	0.9	1	1		97	57	52	53	54	52	50	43	42	42
29	0.6	0.5	0.4	0.7			96	48	37	48	57	53	51	59	53	
30	0.4	0.4	0.5	0.5			97	54	54	34	48	39	22	44	39	
31	0.6	0.6	0.6	0.7	0.7		90	80	60	60	56	59	61	58	59	59
32	0.6	0.6	0.6	0.6			99	60	40	35	35	35	44	42	49	
33	0.8	0.7	0.6	0.8	0.7	0.5	98	70	60	50	47	45	47	40	49	55
34	0.6	0.9	0.9	0.8	0.9	0.9	94	88	56	60	60	49	42	47	49	50
35	0.6	0.6	0.6	0.7			95	90	39	44	54	51	54	45	49	
36	0.8	0.8	0.9				99	32	40	42	50	56	52	42		
37	0.7	0.8	0.5				98	97	48	47	44	42	40	36		
38																
39	0.8	0.5	0.5	0.6			95	89	69	65	60	61	60	63	50	
40	0.5	0.7	0.7	0.5	0.7	0.8	94	66	41	40	39	42	37	42	41	39
41	0.7	0.7	0.7	0.7			98	43	36	28	38	45	42	44	46	
42	0.6	0.8	0.7				94	57	38	42	48	42	48	52		
43	0.8	0.7	0.7	0.6			99	35	36	48	42	42	52	48	48	
44	0.8	0.8	0.9	0.2			98	96	39	44	48	40	41	42	95	
45	1	1	0.9	0.9	0.8		95	92	32	42	56	52	42	44	50	60
46	0.2	0.5	0.2				98	88	37	29	35	28	48	43		
47	0.9	0.7	0.7				96	53	57	52	49	54	54	59		
48	0.7	0.7	0.6	0.5			98	30	32	32	34	38	34	38	48	

49	0.6	0.6	0.8	0.9			98	66	39	43	47	46	48	44	37	
50	0.8	0.6	0.5	0.6			90	45	42	30	33	36	42	44	58	
51	0.7	0.8	0.9	0.6	0.6		89	44	45	35	34	42	41	32	44	40
52	0.9	0.8	0.8	0.9	0.9	1	98	93	40	30	50	62	55	56	63	62
53	0.6	0.6	0.6	0.7			97	46	45	47	47	44	47	48	45	
54	0.75	0.8	0.8	0.7	0.7		90	45	43	39	39	42	43	38	54	58
55	0.8	0.9	1	1			98	42	63	64	65	61	63	62	58	
56	0.8	0.8	0.8	1			96	77	37	43	48	41	38	46	48	
57	0.5	0.6	0.6	0.6			93	67	42	43	48	50	42	40	38	
58	0.6	0.8	0.8	0.8			89	46	39	31	51	57	51	52	53	
59	0.6	0.8	0.6				85	88	36	38	37	37	38	42		
60	0.5	0.5	0.6	0.5			95	46	33	30	40	53	58	48	45	
61	0.6	0.7	0.7	0.7			98	78	35	38	52	48	47	51	56	
62	0.6	0.6	0.6				97	90	35	38	55	24	25	23		
63	0.7	0.7	0.7	0.7	0.8	0.9	97	69	45	42	42	45	49	58	53	58
64	0.9	0.8	0.9				96	79	52	48	42	41	50	47		
65	0.9	1.1	1.1	1			99	89	46	46	49	47	56	46	45	
66	0.9	1	0.7				96	89	53	53	48	47	41	65		
67	0.6	1	0.7	0.9			95	86	57	57	52	61	49	47	42	
68	0.5	0.7	0.6	0.6			98	92	43	37	43	45	44	41	44	
69	0.6	0.5					97	88	38	39	42	47	48			
70	0.6	0.5	0.5	0.5			99	90	53	47	45	41	39	39	41	
71	0.7	0.6	0.7	0.6	0.7		95	80	35	42	46	46	48	48	46	52
72	0.6	0.5	0.6	0.5			93	77	40	44	49	48	55	45	51	

SNO	BIS_5hr	Time_for_awakening_min	Total_dose_fentanyl_ugm_kg	hypotensive_episodes_needed_treatment	No_of_Ephedrin_boluses	Phenylephrine_bolusus	hypertensive_episodes_required_treatment	dose_of_propofol_used_mg_kg	episodes_of_bradycardia	Blood_Loss_ml	Duration_of_surgery_hrs
1		10	2	2	2	0	0	2	0	100	3.5
2		12	2	10	5	5	0	2	0	100	2
3		11	2	1	1	0	1	2	2	300	2.5
4		7	2.3	2	2	0	0	2	0	200	3.5
5		7	2	2	2	0	0	2	0	400	3.2
6		4.5	2	0	0	0	0	0	0	300	3.7
7		8	2	1	1	0	0	0	0	200	3.5
8		7	4	0	0	0	2	3	0	200	2.7
9		8	2.4	4	2	2	0	2	0	400	3.3
10		2	3	6	1	5	0	2	0	200	3.5
11		5	2.5	2	2	0	0	2	0	300	3.2
12	43	10	4	0	0	0	1	3	0	800	5
13		15	4	4	4	0	6	4	0	400	3.5
14		5	2	4	0	4	0	2	0	500	5
15		5	2	0	0	0	0	2	0	250	2.8
16		20	2	13	0	13	0	2	0	250	2.5

17		10	2	5	5	0	1	2.2	0	300	3
18	43	9.5	4	0	0	0	0	2	0	800	5
19		6	2	0	0	0	1	2	0	50	2
20	43	13	3	5	0	0	0	2	0	400	5
21		10	2	7	6	1	0	2	0	150	4
22	42	9	4	15	5	10	0	2.5	0	800	6
23		9	5	5	2	4	1	2	0	400	4
24		17	2	3	3	0	0	2	0	200	2.5
25		7	2	0	0	0	0	2	0	50	2.5
26											
27		15	3	2	2	0	0	3	0	750	4.5
28		2	2	3	3	0	0	2	0	600	4
29		20	2.3	5	5	0	2	2.5	0	150	3.5
30		11	5	0	0	0	5	6	0	500	3.5
31		11	2	11	6	5	0	1	0	500	4
32		13	3	2	2	0	0	1	0	300	2.5
33	62	20	3	7	7	0	3	2	1	800	5.5
34	54	21	4	9	0	9	0	2	0	350	5.5
35		5	3	2	2	0	0	3	0	200	4
36		13	2.5	1	1	0	1	2	1	100	3
37		10	2	1	1	0	0	2	0	200	3
38											
39		5	3	5	4	1	0	4	0	200	4
40	47	14	4	2	2	0	3	4	0	200	5.5
41		10	3	1	1	0	0	2	0	400	3.5
42		5	2	0	0	0	0	2	0	50	2
43		10	2	2	2	0	1	2	0	400	3.5
44		10	3	4	4	0	0	3	0	400	3
45		15	5	0	0	0	5	4	0	900	5
46		7	3	3	3	0	4	4	1	300	3
47		5	3	15	5	10	0	2	0	200	3
48		5	2	0	0	0	0	2	0	250	3
49		3	4	6	6	0	0	3	0	200	3.5
50		10	3	5	5	0	1	2	0	150	3
51		7	4	5	5	0	0	2	0	200	3
52	55	7	4	17	0	17	3	2	0	900	6
53		7	4	5	5	0	0	2	0	200	3
54		8	2	2	2	0	0	2	0	500	4
55		5	4	0	0	0	0	3	1	300	3
56		5	3	4	4	0	0	3	0	350	3.5
57		11	3	0	0	0	2	3	1	300	3
58		8	2	2	2	0	0	2	0	300	3.5
59		5	2	1	1	0	0	2	0	250	2
60		6	2	5	5	0	0	4	0	300	3
61		10	5	2	2	0	2	4	0	200	3

62		15	2	5	5	0	0	2	0	300	3
63	42	10	6	6	6	0	0	5	0	1500	6
64		13	3	2	2	0	0	2	0	200	3
65		5	4	1	1	0	0	2	0	200	4
66		6	3	5	5	0	0	2	0	200	2
67		20	4	0	0	0	5	4	0	500	4.5
68		5	4	0	0	0	0	3	0	200	3
69		3	4	3	3	0	0	2	0	50	2
70		10	3	1	1	0	0	2	0	400	3.2
71		5	4	9	9	0	0	2	0	400	4.5
72		6	3	0	0	0	0	2	0	300	3

INSTITUTIONAL REVIEW BOARD (IRB)
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VELLORE 632 002, INDIA

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Secretary, Ethics Committee, IRB
Additional Vice Principal(Research)

January 31, 2012

Dr. Hari Narayana Prabhu
Department of Anaesthesia
Christian Medical College
Vellore 632 004

Sub: **FLUID Research grant project NEW PROPOSAL:**
A randomized control trial to compare the effect of dexmedetomidine infusion in the perioperative period Vs oral clonidine as premedication, on anaesthetic requirements, haemodynamics and recovery from anesthesia in patients undergoing major spine surgery
Dr. Hari Narayana Prabhu, Anaesthesia, Dr. Ramamani, Dr. Grace Korula, Dr. Balaji Anaesthesia.

Ref: IRB Min. No. 7688 dated 23.11.2011

Dear Dr. Prabhu,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A randomized control trial to compare the effect of dexmedetomidine infusion in the perioperative period Vs oral clonidine as premedication, on anaesthetic requirements, haemodynamics and recovery from anesthesia in patients undergoing major spine surgery" on November 23, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English, Tamil and Hindi)
3. CVs of Dr. Ramamani Mariappan, Hari Narayana Prabhu, K. Balaji
4. A CD containing documents 1 – 3

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
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Chairperson, Research Committee & Principal

Dr. Gagandeep Kang, MD, PhD, FRCPath
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal(Research)

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on November 23, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliation
Dr. Prabhakar D Moses (on behalf of Dr. Lionel Gnanaraj)	MBBS, MS, M.Ch. (Urol)	Medical Superintendent, CMC.	
Dr. Prathap Tharyan	MD, MRCPsych.	Associate Director, Professor of Psychiatry, CMC	
Mrs. Mary Johnson (on behalf of Mrs. Dr.Jayarani Premkumar)	M.Sc. (Nursing)	Nursing Superintendent, CMC.	
Mrs. Shirley David (on behalf of Mrs. Rosaline Jayakaran)	M.Sc. (Nursing), RN, RM	Dean, College of Nursing, CMC.	
Rev. Malhia Joshua	MA, MEd, MTh, PhD	Chaplain, CMC	
Mr. Harikrishnan	BL.	Lawyer	Non-CMC
Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology Dept CMC.	
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC
Dr. P. Zachariah	MBBS, PhD	Retired Professor , Vellore	Non-CMC
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Resea CMC.	

We approve the project to be conducted as presented.

The Institutional Review Board expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
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Dr. Alfred Job Daniel, MS Ortho
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Dr. Gagandeep Kang, MD, PhD, FRCPath
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal(Research)

A sum of ₹ 66, 310/- (Rupees Sixty six thousand three hundred and ten only) is sanctioned for 2 years.

Yours Sincerely

Gagandeep Kang, MD, PhD, FRCPath
Secretary (Ethics Committee)
Institutional Review Board

Secretary
Institutional Review Board
(Ethics Committee)
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

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